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INCREASING THE PRODUCTIVITY OF RESEARCH[1]

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VERY few scientists have had opportunity during the past five years of engaging in research of their own interest and choosing. The demands of war have placed urgent emphasis on the need for developing practical embodiments of scientific principles with the purpose of providing our armed forces with all manner of new devices more potent in warfare than those of the enemy. To this end, the great majority of our scientists and engineers in university and industry and in the laboratories of government departments have been united in a common effort, on a scale without precedent, bringing to bear upon the problems presented a vast resource of ingenuity, drawing upon an equally vast store of scientific knowledge and practical experience. Their accomplishment will speak for itself when security regulations will no longer prevent disclosure. It is matched only by the miraculous accomplishment of American industry in producing the equipment and supplies by which our armies and navies and those of our allies have so competently brought their tasks of unprecedented magnitude so near successful conclusion.

The productivity of our scientists and engineers in the war effort has been possible because of the large numbers engaged in work of common character; the unlimited funds and facilities available for the work; and the strong stimulus of doing something potentially valuable in helping to win the war. To those who have had opportunity of seeing many aspects of war research, it is apparent that most of

[1] Delivered before the Northwestern University Chapter, Society of Sigma Xi, Evanston, Illinois, May 18, 1945.

the activity has been developmental. Its contribution to fundamental knowledge has been small. Rather, in a manner of speaking, it has been eating into our reserves of fundamental knowledge and has been making applications of that knowledge to destructive purposes. Although we admit this with extreme regret—regret that the greatest effort in scientific activity that the world has ever known has had to do with destruction and devastation—there has been no alternative. But the time has come when we may again think and plan in terms of peaceful pursuits, with the hope and expectation that the results of our future efforts may be beneficial and restorative and contribute to human welfare and contentment.

The word research has been defined in many different ways, depending, perhaps, on the interests and associations of the person writing the definition. The kind of research that has as its objective new developments for industry is whimsically defined by C. F. Kettering as "the process of finding out what we're going to do after we can't keep on doing what we're doing now." That definition, though pointed and epigrammatic, does not quite meet the needs of this discussion. In order that we may have a common understanding of the meaning of the term, I should like for our purposes to propose the following:

Research is original and creative intellectual activity carried on in the laboratory, the library or in the field, which endeavors to discover new facts and to appraise and interpret them properly in the light of previous knowledge. With constantly increasing understanding, it revises previously accepted conclusions, theories and laws, and makes new applications of its findings. Whether it seeks to extend knowledge for its own sake or to achieve results with specific economic or social value, its *raison d'être* is its contribution to human welfare.

Having established a definition of which most of you would approve, let us get on with our subject, "Increasing the Productivity of Research." The implication of this title is that there is need for enhancing and augmenting the results of effort devoted to research. Although we may wishfully hold the opinion that support for research should be unlimited, or that the need for such support should not be questioned, it must not be forgotten that in the last analysis funds for conducting research are provided by the public, whether the channels through which they flow are those of government, commerce, industry or, indeed, whether they are gifts from private sources. That research needs doing need not be argued. Its results, so far as modern living is concerned, envelop us, and speak for themselves. But are we in position to argue that the effect upon the world would be disastrous unless some annual quota of research output were reached? Obviously not. What we can and do say is that the greater and better the output, the more will the world benefit by the results, and the more rapid will be our climb towards better living—better in the broadest meaning of that word. Nor can there be any doubt that we must continue to add to our reserves of fundamental knowledge, and that need will arise in many directions to apply existing knowledge as well as newly acquired knowledge to immediate problems. As the problems of war are left behind, and postwar activities are undertaken, the first great change that the many thousands who were engaged on government contracts will notice is the necessity for readjustment to a greatly diminished scale of support. Another change is that the pressure to get the job done will have been much reduced. We shall again be pursuing our work in more leisurely fashion and shall have time for the meditative and reflective aspects of investigations without the inevitable interruptions that the abnormal conditions brought upon us. Notwithstanding the reduced pressure and the consequent improvement in environment for scholarly endeavors, we are in agreement, I am sure, that research should be conducted with the purpose of achieving the best results both in quality and quantity in relation to the available time and the effort and money applied to it.

As we view the postwar picture we shall discern quickly that the number of competent research workers will have become greatly diminished during the war years, by death and retirements at one end of the age scale, and by almost complete cessation of replacement at the other. This question has been discussed in a number of recent articles. It is a subject of many implications, which must be of much concern to scientists. We lack time to treat it extensively. My only purpose in bringing it into this discussion is to introduce the fact that in our postwar research there will be a period of perhaps ten years in which we shall have far fewer research workers than our institutional and industrial laboratories will need. This is one factor that bears on the problem of increasing the productivity of the individual doing research.

As we consider quantity and quality of research, we feel keenly the need for some way of measuring the output. The only unit we seem to have, and which is patently not a measure of output, is the number of dollars that support it. Numbers of pages of published results are sometimes used as a gage of scholarship upon which advancement in professional status depends. To my knowledge, no one has ever found a formula for converting this number of pages to a figure of merit of the work set forth in the pub-

lications. The evaluation of results of research, from the standpoint of human welfare and benefit, has, in short, not been reduced to measurement. We can therefore speak only in relative terms and say that we hope for more and better research, or that our output of valuable results per dollar ought to increase. That this hope is justified rests on the conviction that the point of diminishing return per dollar spent has not been reached, that we are, in fact, far from it, and that it is not likely to be reached within predictable time. Thus it appears self-evident that all possible means to increase the effectiveness of our research should be employed. I should like to explore with you some means for accomplishing this purpose.

It is generally recognized that progress in science is intimately associated with and dependent upon availability of instrumental aids for observation, measurement and control. To this thesis, Zeleny[2] devoted his retiring address as vice-president of the American Association for the Advancement of Science and chairman of Section B in 1916. In the industrial field, the word "instrumentation" has come to mean the control, by means of instruments and devices based on measuring techniques, of industrial processes. I should like to introduce a new and broader term—"instrumentology"—a contraction of "instrumental technology"—to denote the science and art of applying instruments, and methods used in association with instruments, to extending our powers of observation, to the making of accurate measurements, to the precise control of ambient conditions and to the analysis, reduction or other processing of data.

If you are an Einstein or if, perchance, your field is theoretical physics or pure mathematics, the only equipment you will need is pencil and paper. The great majority of scientists are, obviously, not Einsteins; nor are they theoretical physicists or mathematicians. Even in these categories, the validity of paper-and-pencil research, except, perhaps, in the field of pure mathematics, can not be established without the use of instrumental methods.

Three decades ago it was still possible for the individual research worker, in most fields, to familiarize himself with instrumental methods that might be of use to him in his own researches and, with some months of application, to become reasonably expert in applying the chosen instruments to his problems. During the past three decades, however, the field of instrumentology has become so complex and has advanced with such speed that no individual scientist could hope to keep pace with even a small section of the advancing technology. It hardly needs pointing out that instrumentology makes applications primarily of physical principles. Yet there is not a physicist, I dare say, who is intimately familiar with the principles and the details of all the instruments that have been described or that are available for all the kinds of measurement, observation and control that might find useful application in the research laboratory. Since instruments make applications of fundamental physical principles, the physicist may be in somewhat better position to comprehend broadly what is possible with instruments, what is available for use, and, in general, how they may be applied to specific problems.

If the physicist, in whose domain the principles of instruments lie, can not hope to keep currently abreast of instrumental developments, what shall we say about the biologist or the psychologist or the engineer or the research worker in medicine whose researches distinctly call for an application of instrumental methods? Unless the biologist happens to be a biophysicist, the psychologist a psychophysicist, the geologist a geophysicist, or the chemist a chemical physicist or physical chemist, it is unlikely that in the course of his training or experience he has acquired more than a nodding acquaintance with instrumentology. If in his—let us say, biological—research problem the application of instruments is clearly indicated, what course should he pursue?

He thinks his problem through. In this reviewing process it occurs to him that his friend Jones in the department of physics is more or less expert in this particular field which may call for the application of electronics to the precise control of some particular environmental condition. He goes to see Jones and talks the problem over with him, hoping, but not expecting, that more aid than a few helpful comments will be forthcoming. His negative expectation is realized. Jones, the physicist, has his own problems. He is courteous and friendly and helpful enough, to a point, but beyond that, Smith, the biologist, has to shift for himself. Fired with enthusiasm and zeal to get into his problem and make headway with it, he studies the references that Jones has given him, and after some weeks of intensive application he feels reasonably qualified to go ahead, employing an instrumental procedure that he hopes will do the job. Unfortunately, the particular instrument that he has decided upon using is not regularly available from the dealer in scientific instruments. If it were, the chances are that Smith's research would have been done long ago. He is working in a new field in which biology and physics overlap and, consequently, no specific instrument has been devised for the application he has in mind. So he sets about designing the instrument, with occasional help from Jones in selecting the proper components for the electric circuits and, perhaps, an optical system, and after some weeks more the device is put together and, with sufficient

[2] Science, 43: 185, 1916.

"debugging and doctoring," it is made to operate, after a fashion. Smith has spent several months doing things that he should not have to do, things with which he is not particularly familiar or particularly expert. He finally gets his research under way. Although the instrument falls a bit short of his expectations, he eventually gets his results and publishes his paper. In all probability the research turned out less well than it might have, had he been in position to devote his entire time to intensive study of the problem in his own field of specialization.

Now let us take another view of the same problem. The university with which Smith is connected is a fairly large, well-established institution. The administration has accepted the truism that a university has the traditional obligation to the public to foster and facilitate research among the scholars who comprise its faculty. It has established adequate libraries to enable its scholars in the non-laboratory fields to do distinguished work. It has also recognized that for equally distinguished work in the many fields that depend upon instrumentology there must be available the facilities for providing and applying such methods. There has consequently been established a group of research service centers, including a laboratory headed by Brown, a specialist in electronics, for whom it is as simple to design a circuit for a specific purpose as it is for Smith the biologist to plan a problem in which the use of paramecium or drosophila is indicated. Smith is aware that one of Brown's assigned functions is to consult with men like Smith, to assist them in devising the electronic aids for carrying on their researches. Brown has in his laboratory several technicians trained in putting electronic circuits together and making them function properly. After discussion with Smith, he directs one of the technicians to build a device which he then turns over to Smith; more than that, he assigns the technician to assist Smith in putting it in operation and use. Smith has been saved a number of months of study and effort in a field in which he is not a specialist and in which he is not particularly interested, and has saved the time for the effective application of his greater knowledge of his own field.

The word picture I have just given will, I think, offer an insight into a proposal which should be considered in every university that extensively supports scientific research. It will also suggest a plan which I am confident will vitalize scientific research in a university and materially increase the valuable output per dollar of the funds that support its research.

A group of research service laboratories of the kind that assisted Smith in his problem is, in my opinion, potentially the most effective agency that can be devised for assisting research in all departments of science. *They are the laboratories of instrumentology, whose work constitutes a technology consisting of the application of science to science itself.* Under this plan a university would have available a group of specialists able and ready to consult with any research worker in the university, whether in pure or applied science, engineering or medicine. These specialists would assist the research worker not only with advice but by the loan of qualified personnel, either to familiarize the research worker himself with a method or procedure, thereby enabling him to carry on without further assistance; or, in the case of the highly specialized, complicated instrument, to operate the instrument.

It would be wearisome for you to have to listen to a portrayal of details of all the laboratories that might comprise such a group. A quick review of some possibilities, with brief comments, may prove interesting. I would not confine the subject-matter of the laboratories to physics because there are techniques and procedures in chemistry and mathematics, for example, that are as much a part of instrumentology as are the techniques of physics. In the Office of Scientific Research and Development it was found not only valuable but essential to establish a group of mathematicians, known as the Applied Mathematics Panel, to assist the research workers in the various fields of activities covered by the National Defense Research Committee. It is equally important in peacetime research to have mathematical aid for research in the sciences, in economics and in other fields.

I would therefore place on my list of research service centers a laboratory of applied mathematics, equipped with all the latest calculating machines and devices for which research in the university might find need. Working closely with it, and possibly cooperating in the design and development of new mechanical, optical or electronic means for performing complicated mathematical operations, might be a laboratory for specialization in methods of control, including such war-tested indispensable devices as servo-mechanisms. There would be a laboratory specializing in microchemical techniques; another one employing the instrumental facilities that have proved so effective in physical chemistry and electrochemistry. To keep abreast of the important new developments of materials there would be a laboratory of metallurgy and metallography, another dealing with the technology of plastics and wood, another with fibers and textiles, still another specializing in high-polymer physics and chemistry. In these four laboratories would be found men with qualifications to handle all problems having to do with the properties of materials; they would have particular significance in many aspects of engineering.

Still another group would deal with meteorology and geophysics, the latter presumably having much potential value for a department of geology which realizes that great progress is possible in the application of physical methods to its problems. There would be a laboratory specializing in problems of heat and temperature and the measurement and control of these quantities, and one dealing with problems of vibration and acoustics. There would be a laboratory specializing in the applications of such techniques as measurement of relative masses of atoms and molecules with a mass spectrograph. Another would deal with spectrography and spectrophotometry, extending through the visible and the adjacent invisible regions of radiant energy. There would be laboratories specializing in applied optics, including polarimetry, photoelasticity and applications of photography as well as other uses of optics in research. Applications of electrical measurement and control, of electronics and gaseous conduction, of x-rays and radioactivity, would constitute a group of technologies employing the developments particularly of the past several decades. Others would be established as the need arose and new methods and procedures became available.

One of the laboratories mentioned would be equipped with an electron microscope. This instrument has found diversified applications; but since its cost, and at present its size, are such that it would hardly be feasible to provide an electron microscope for every department of a university that might use it, an instrument centrally available would serve an exceedingly useful purpose for many departments and many kinds of research. In charge of the microscope would be a technician who has been thoroughly trained in its use and who could therefore apply it to any particular problem to best advantage. The same thing may be said about a mass spectrograph, perhaps a betatron, and other instruments similar in kind.

Associated with such laboratories there would be all the shop facilities required to render their work effective. The shop would be equipped with precision tools for the working of metals, wood, plastics, glass and other materials useful in research. The shop, indispensable and invaluable to the laboratories, would provide personnel specially trained in general laboratory techniques, such as setting up optical systems, vacuum systems and systems for maintaining pressure, rates of flow and other quantities at desired levels. Its superintendent or an assistant would aid in developing the mechanical designs of special apparatus with reference to simplicity and ease of construction.

You will before now have detected the principal difficulties in making such a plan work effectively. One of these is the problem of finding and assembling a well-qualified staff endowed with sufficiently broad vision and understanding to appreciate the important part it can play in the advancement of science. A university administration, as well as a directing head of such a group of laboratories, must realize that these are as essential to research in science as is the research library to the non-laboratory fields of scholarship. The scientist responsible for any particular laboratory must have understanding of and be sympathetic with the problems of the scientists in fields other than his own. His value is enhanced if he familiarizes himself with the general aspects of the several fields of science that his laboratory has been established to serve.

Another, and the only other major problem that may impose difficulty in carrying such a plan to successful realization, is that of kudos for the scientists who comprise the staff of the laboratories. The person responsible for any one of the fields will of necessity devote some of his time to the problems of his colleagues in the university. He may or may not develop material suitable for publication, to show for the time thus spent. But, on the credit side of his picture, is the fact that his own research will consist in extending his technology to the problems that will either be presented to him or that he himself may find and suggest to the specialists in the field in which that problem falls. The extension of his technology, together with the development of new and improved instruments within his field, will be his research. More than that, however, may be confidently expected. His own horizon will expand, and he will discover problems that would not otherwise occur to him.

As such laboratories come into existence and begin their activity in the service of science in a university, more and more researches will develop in those areas in which contiguous sciences overlap. Here the specialist in instrumentology and the scientist with whom he joins his interests will become co-workers and joint authors of papers describing the results of their cooperative research. The problems brought to the instrument specialist by scientists from fields outside his own will stimulate his interest and imagination so that he becomes more productive in his own field. There lies ahead also the strong probability that the scientist who has been assisted by one of the laboratories of instrumentology will develop an output of research with higher quality and greater frequency than would be remotely possible for him with equal effort spread over activities with which he should not have to concern himself.

The proposed plan is capable of stimulating and developing the research potential in another way. The training of students in the theoretical funda-

mentals, in the scientific method and in the practical applications of the scientific method employing the powerful tools of instrumentology—such training can make great contributions to research in a long-range program. The conduct of such training might logically become the responsibility of a department of applied science, which would also be the logical responsible agency to conduct the activities of the laboratories of instrumentology. Basic courses in mathematics, physics and chemistry, in such concentration as might be supported in the curriculum, would constitute its foundation. All these courses would be planned in cooperation with and offered by the departments representing these several fields of knowledge. In parallel with the fundamental studies there would be general and specific courses in instrumentology, with supporting electives. These would be enriched and broadened and liberalized by courses chosen for that purpose, and it need hardly be added that sufficient training in English would be included to assure ability to express ideas clearly. This plan would provide training of a kind not now available. It would provide foundations of education for biophysicists, and for physicists with intensive training in other directions, such as petroleum technology, metallurgy, acoustics and optics, to cite only a few examples. A student who had completed work to the bachelor's or master's level in such a curriculum would be well prepared for service in many kinds of industry. He would be equally well prepared for graduate work looking towards advanced degrees.

This discussion of the training of students tempts me to digress long enough to put before you a brief outline of what seem to me to be the objectives of education—an outline that I would use as a general guide in conducting the kind of course I have in mind. During an industrial interlude of more than twenty years my interest in education never faltered, resting as it does on the firm conviction that the hope of a better future lies in better education and better research. The outline, crystallized out of personal experiences, out of a great deal of time available for thinking while traveling endless hours during the past five years, and out of many discussions with educators, directors of research, personnel directors and government scientists, is an attempt to set down these objectives in a single typewritten page. Please observe that no distinction is made between "liberal" and "technical" education. For this failure to distinguish, if failure it be, I offer no apology; I have been unable to persuade myself that education should have restrictive labels.

The objectives of education are to develop knowledge, the arts, manners, and wisdom.

Knowledge is a comprehension of information, facts and theories, and an understanding of interrelationships among them. It is acquired most effectively by thoughtful reading, discussion and observation, and by the development of good habits of study through the exercise of self-discipline. Methods of acquiring knowledge are more important to the student than knowledge itself.

The *Arts* are the "know how" of doing. They can not be learned by reading. They are acquired under competent guidance and direction, with ample opportunity for the student to train himself and to develop his creative talents, curiosity, imagination and ability to think. Much of the content of education is knowing how to do things; it is ability to apply mental and manual dexterity, and to plan and direct the attack upon a problem. Applied mathematics and applied science are examples of the advanced arts; so is applied English—the ability to write a report with clarity and brevity. Many problems of the future will demand both knowledge and the arts at high levels of attainment.

Manners, in its simplest aspect, is social behavior—the attitude of the individual towards others. The development of good manners depends in larger degree upon example and advice to the student by members of the faculty who themselves have attained a high level of social behavior than it does upon formal courses. Cultural subjects, such as history, philosophy, economics and sociology, contribute to such development, and assist in providing unification and integration among the several factors that comprise education. The student should acquire a consciousness of his obligations to society, and of the indispensability of personal integrity and responsibility in his dealings with others. Home and community influences are perhaps more potent in the development of good manners than anything that school or college can do.

Wisdom is the attribute exemplified by sound judgment and common sense. It governs the way in which knowledge, the arts and manners are applied in any particular situation. An indication of wisdom is the ability to appraise a set of circumstances, to foresee their implications, and to initiate action that will assure attainment of desired ends. Since wisdom depends for the most part on an inherent aptitude, or "native intelligence," formal education can not beget wisdom, nor is its possession a monopoly of those who have had formal education; but the educational process can be significant in its development. Experience with things and people enriches wisdom.

If the educating process achieves the objectives of imparting knowledge, and developing the arts, manners and wisdom in a student, it may be accounted successful.

To resume the main theme, it is my strong conviction that the establishment of a department of applied science in a university, designed to train students in research, and to serve the various departments of science, medicine and engineering, will find even greater opportunity for public service in the fact that it will render the output of the various departments more significant not only as regards fundamental knowledge but also in the application of such knowledge to specific problems. The specific problems for the most

rt will arise in industry and come into the university research projects in which the university and industry participate, on a cooperative basis. Research increase fundamental knowledge and research to pply that knowledge will thereby be enriched, the imediate beneficiaries being the university and indusy, and through them, the public. Thus, the estabshment of a department of applied science in a uniersity, along the indicated lines, would, in relation effort and expenditure, do more to vitalize and stimlate research, both fundamental and applied, than ny other comparable measure; and its output of wellained graduates and postgraduates would make a further major contribution towards increasing our total output of results at high levels of quality.

I am not unaware that the picture I have tried to present of a department of applied science, with its laboratories of instrumentology, may remind some of you of certain passages in Revelations, describing visions of a great city of white marble, in which the streets are paved with gold. Should that be your impression, my comment is that without vision we shall make no progress; and if, perchance, we are granted vision, shall we not think in terms sufficiently inspiring to set a goal for which it will be worth our while to strive?

OBITUARY

WILLIAM HENRY HOWELL
1860–1945

The death of Dr. William H. Howell on February , 1945, marks the passing of the first group of proessional physiologists in the United States, and of he galaxy of talent entrusted with the organization f the departments of the Medical School of the Johns Hopkins University prior to the opening of its doors o students of medicine in 1893. With his death America has lost one of the leading figures in physioogical science.

William Henry Howell, born in Baltimore on Febuary 20, 1860, was the son of George Henry and Virginia Magruder Howell. William Henry was eduated in the public schools of Baltimore. In his enior year at City College, as the Baltimore high school is designated, he left school to become assistant to the professor of physics and chemistry. In the fall of 1878 he entered the Johns Hopkins University as an undergraduate student in the chemical-biological course to prepare himself for the study of medicine. Upon his graduation in 1881 he was awarded a graduate scholarship and because of this he matriculated in the graduate school as a candidate for the degree of doctor of philosophy, instead of following his original intention to study medicine. However, while pursuing his graduate studies he took extramural courses in anatomy and attended clinics at the Medical School of the University of Maryland. He was awarded the Ph.D. degree in 1884.

In 1885 he was made chief assistant in biology under his teacher, Newell Martin. Subsequently he was promoted to the grade of associate and, finally, associate professor of biology, in which capacity he gave the lectures in animal physiology in the undergraduate courses. In 1889 he was appointed lecturer and in 1890 professor of physiology in the University of Michigan. In 1892 he accepted appointment as associate professor under Dr. H. P. Bowditch at the Harvard Medical School and in 1893 he became the first professor of physiology of the Medical School of the Johns Hopkins University.

For twelve years, from 1899 until 1911, he served as dean of the Medical School, succeeding Dr. Welch, the first dean. When the School of Hygiene and Public Health of the Johns Hopkins University was founded in 1918 he severed his connection with the Medical School to accept appointment as assistant director and professor of physiology in the School of Hygiene. Eight years later he succeeded Dr. Welch as director of that school. He retired in 1931, but was provided with a laboratory by the university and, with funds supplied first by a research foundation, and subsequently from the fluid research fund of the Medical School, he continued with research almost to the day of his death, though he knew he had arteriosclerosis and was having some heart attacks. At 5:00 A.M. on February 6th he was seized with a severe attack and died almost immediately. His mind retained its pristine clearness to the end.

Throughout his career Dr. Howell's prime interest was research, though he never allowed that interest to interfere with the meticulous performance of his duties as teacher and as administrator. He was deeply but, to all appearances, calmly absorbed in his research problems. The conduct of his researches seemed unhurried, even when conversation indicated that interesting developments were imminent. Though research was the occupation that gave him his greatest satisfactions, one gains the impression from statements he has made that it was for him at the same time a discipline. Yet he never turned over any of the detail to others; he never at any time had a trained research assistant. Whatever turn a problem took, whether into physics, as when he was dealing with fibrin crystals, or into chemistry, as when cephalin and heparin were isolated, he acquired and carried through the necessary techniques. Even after his retirement he

declined offers of technical assistance. "I'd get along faster," he is reported to have said, "if I got an expert organic chemist to work with me, but it is more fun to do it myself."

Howell's scientific publications include some eighty titles. Starting as a student of Newell Martin, it was but natural that his attention would be attracted to the fields that interested his teacher, namely, the physiology of the heart, of the circulation and of the blood. And so we find that Howell's first papers deal with the heart beat and with certain aspects of the physiology of blood; indeed, coagulation of the blood and the physiological action of the salt content of the blood can be regarded as his major fields of research.

One of his earliest contributions consisted in showing that serum albumin is not essential to the nourishment of the heart, as had been asserted by European physiologists, but that it was the inorganic content of their perfusion solutions that had maintained the beat of the heart. It was his interest in salt action that led to the demonstration by him of the possible significance of potassium as an inhibitor of the heart. Potassium is now known to be intimately connected with at least some of the acetylcholine mechanisms of impulse transmission. However, its exact role in that process remains to be determined.

Howell's name is conspicuously identified with the investigation of the process of blood coagulation; he is credited, among many other significant findings, with the isolation of some of the more important chemical factors that play a role in coagulation, such as cephalin and heparin. At the age of 77 he published a finding of the greatest interest, namely, that in extrauterine life blood platelets, a source of cephalin, are formed primarily in the lungs; and just prior to his death he was busily investigating a new blood coagulant.

The position Dr. Howell occupied in American physiology may be evaluated by the recognition accorded him by his colleagues. He was one of the twenty-eight charter members of the American Physiological Society and, excepting Hare and Jastrow, was the youngest of the group. To him was accorded the honor of reading the first paper at the first meeting of the society. He was its third president and was younger by many years than were either of his predecessors at the time they served in that capacity. He was re-elected to the office five times. He was chosen by the American physiologists to be the president of the first and only International Physiological Congress to meet in the Americas. He was editor of the "American Textbook of Physiology," published in 1896, the first cooperative effort of the kind on this side of the water. He was a member of numerous national honor societies and an honorary member of several foreign societies. He was the possessor, also, of a number of honorary degrees, including his M.D. degree, which was given by the University of Michigan.

One of Dr. Howell's striking personal characteristics was a mildness and cheerfulness of manner, yet he held firm but carefully weighed convictions. They were never, however, obtruded on casual acquaintances. His strength of intellect, his wisdom, his moral fiber gave him the peace of mind and the sympathetic understanding of his fellow men that were so apparent to all who knew him well. He enjoyed particularly the simple things in life—music, the out-of-doors and the comradeship of his family. He possessed a remarkable ability to express his thoughts in conversation, in the classroom and before assemblages, whether scientific or general, with a directness and a simplicity of verbiage that invariably charmed his hearers. He will be remembered not only as an accomplished and meticulous investigator; an inspiring teacher and as an able and considerate administrator, but equally for his personal attributes—a calm, simple philosophy of life and the ability to live in the light of that philosophy.

JOSEPH ERLANGER

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EDWARD O. SPERLING

IN the closing words of many a scientific paper there will be found a heartfelt tribute to some skilful artisan, heartfelt because the author knew that the artisan's skill was beyond his own. Glass-blower, instrument maker, optician, these craftsmen have all played their part in the advancement of science and indeed have made many a brilliant research possible.

Edward Sperling was a master craftsman in the art of blowing glass. Joining the staff of the National Bureau of Standards in 1907, he devoted his skill for the succeeding thirty-eight years to the construction of equipment which would facilitate the bureau's work. Recognition of his ingenuity and masterly workmanship quickly spread beyond the confines of Washington. Scientists the country over asked for his help in constructing equipment that was beyond the skill of other men. Although his formal education did not go beyond that of the public schools, the Civil Service Commission gave him in his later years a unique professional status comparable with that of scientists holding doctorate degrees. He was in truth the dean of his profession in Washington.

The last rites were said for Edward Sperling on May 14 in the presence of bureau scientists with whom he had worked for years. The importance of his contributions in helping others can hardly be overemphasized. Laboratory after laboratory bears in shining glass mute evidence of his skill. But the

bureau staff will cherish likewise those admirable qualities of the man himself that so endeared him to his friends.

LYMAN J. BRIGGS

WASHINGTON, D. C.

RECENT DEATHS

THE death, at forty-three years, is announced of Dr. Albert H. Palmer, of the University of Toronto, formerly of the department of agricultural biochemistry of the Pennsylvania State College.

GEORGE T. SEABURY, since 1925 secretary of the American Society of Civil Engineers, died on May 25 at the age of sixty-five years.

DR. FREDERICK WILLIAM SHAW, professor of parasitology at the Medical College of Virginia, Richmond, died on May 29 at the age of sixty-two years.

SCIENTIFIC EVENTS

THE TECTONIC MAP OF THE UNITED STATES

A TECTONIC map of the United States was published in November, 1944, and is now on sale by the American Association of Petroleum Geologists.[1] In simple terms a tectonic map is one that depicts by symbols and patterns the geologic structure—that is, the lay of the rock strata, their folds and dislocations, and the position of volcanoes, salt domes and many other features.

The map has been in great demand during the five months since its publication, which suggests that geologists have previously felt a need for one and for the new viewpoint which it gives them on many geologic problems. Geologic maps which show the distribution of rocks at the surface are readily available, and one of the United States was published by the Federal Geological Survey in 1933. Tectonic maps which show the structure of these rocks, and of others underground, have been made before. These were mostly of small areas, and if larger areas were dealt with the maps were on a small scale. The present tectonic map, which measures about four by seven feet, is the first to show the geologic structure of a large part of the North American continent in considerable detail and on a reasonably large scale.

The tectonic map of the United States is the result of long planning and cooperative endeavor by American geologists and their organizations. It was compiled by the Committee on Tectonics of the National Research Council. The map was conceived when the committee was first organized in 1922, but actual work on it was not started until 1934, when Professor C. R. Longwell, of Yale University, assumed chairmanship of the committee. As organized by Dr. Longwell, the committee was a representative group of American geologists, including members from all parts of the country, and from the Federal Geological Survey, the state surveys, the universities and the petroleum industry.[2] The first compilation of copy was completed in 1940, and corrected copy was ready in 1941. War conditions slowed the final editing, drafting and printing. The American Association of Petroleum Geologists undertook to finance the publication and distribution, partly because of the great interest which the map holds for petroleum geologists and partly because other possible publishing organizations were engaged in wartime duties.

The tectonic map is based in part upon published sources and in part on material that had not hitherto been published. Among the published sources are the numerous maps issued by the Federal Geological Survey. A large amount of unpublished material was furnished by petroleum geologists. On the map, the structure of the gently tilted rocks of the central interior region and the eastern and southern coastal plains is represented by structure contour lines. To a large extent these contours are derived from data obtained in the drilling of numerous wells put down in the search for oil and gas. This material was assembled with the aid of committees of the American Association of Petroleum Geologists and of the local societies of petroleum geologists.

A tectonic map is of more than academic interest. Geologists searching for ore deposits and petroleum must strive to open up new productive provinces as well as to extend the old ones. Local surface indications are by now thoroughly known, so that the approach is increasingly through the more subtle study of broad regional indications and conditions. Knowledge of the regional geologic structure is vital in such studies, and the tectonic map is a useful source for this information. Although the tectonic map was not conceived as either an economic or a war project, the wide use which has already been made of it in exploration for commodities needed in time of war is a source of satisfaction to all the members of the Committee on Tectonics.—PHILIP B. KING.[3]

[1] Inquiries regarding purchase of the map should be addressed to the American Association of Petroleum Geologists, Box 979, Tulsa, Oklahoma.

[2] Members of the Committee on Tectonics are C. R. Longwell, *chairman*, P. B. King, *vice-chairman*, C. H. Behre, Jr., W. H. Bucher, Eugene Callaghan, D. F. Hewett, G. M. Kay, Mrs. E. B. Knopf, A. I. Levorsen, T. S. Lovering, G. R. Mansfield, W. H. Monroe, J. T. Pardee, R. D. Reed, G. W. Stose, W. T. Thom, Jr., A. C. Waters, E. D. Wilson and A. O. Woodford.

[3] Geologist, Geological Survey, U. S. Department of Interior; vice-chairman of the Committee on Tectonics, National Research Council. Published by permission of the director of the Geological Survey.

THE PERUVIAN INSTITUTE OF CHEMICAL ENGINEERS

A MEETING of chemical engineers was held at the "Sociedad de Ingenieros del Perú" in September, 1944. At that meeting it was decided to constitute the Peruvian Institute of Chemical Engineers. The next three months were dedicated to the study of the constitution that was to guide the destinies of the institute; using wherever possible the constitution of the American Institute of Chemical Engineers.

Finally in December the first regular meeting was held. At that meeting the constitution was approved and it was decided that the institute should be known as Instituto Peruano de Ingenieros Químicos. Officers were nominated for the 1945–1947 period as follows:

President, Alfonso Montero.
Vice-president, Carlos Díaz-Ufano.
Secretary, Joaquín Vargas.
Treasurer, Luis Macchiavello.
Librarian, José María Cancino.
Directors, Manuel Yábar and Juan Vicente Cabrerizo.

The institute has already been incorporated under the laws of Peru, and also has been officially approved by the Peruvian Government.

The objects of the institute are to promote friendship among members of the profession; to promote the application of chemical engineering principles in the national industry; to improve methods of teaching chemical engineering; to set forth rules to guide the acts of its members; and to maintain scientific and cultural interchange with technical institutions in foreign countries.

There are four different categories of membership: Active members are graduated chemical engineers from universities of recognized standing who have their degrees registered as established by the Peruvian laws. Pre-active members are those chemical engineers who have not yet officially received their degrees, but who have completed their period of learning; a member can not hold the pre-active membership over two years. Associate members are those individuals holding the degree of industrial engineer, highly specialized in a chemical engineering field. Student members are the students of the fifth year in the "Escuela Nacional de Ingenieros."

At present there are only thirty-two members. Election for membership is not only for Peruvian citizens, but also for foreign chemical engineers holding a degree from a university of recognized standing.

JOAQUÍN VARGAS,
Secretary

THE WORCESTER FOUNDATION FOR EXPERIMENTAL BIOLOGY

THE dedication of the Shrewsbury Laboratories of the Worcester Foundation for Experimental Biology will take place at Worcester, Mass., on June 9. The ground on which the institution stands, the buildings and the equipment were purchased through funds contributed by the community of Worcester and Worcester County.

Dr. Harlow Shapley, director of the Harvard College Observatory, is president of the foundation. The scientific work is under the direction of Dr. Hudson Hoagland and Dr. Gregory Pincus, who is director of the laboratories. Among the trustees are Dr. Roy G. Hoskins, director of the Memorial Foundation for Neuroendocrine Research of the Harvard Medical School; Dr. William J. Crozier, professor of general physiology at Harvard University, and Dr. Wendell M. Stanley, member of the Rockefeller Institute for Medical Research at Princeton, N. J.

The foundation was incorporated in February, 1944, as a non-profit research and educational institution under the laws of the Commonwealth of Massachusetts. Its purpose is to make investigations at the discretion of its directors in the field of the biological sciences and publish the results of these investigations in scientific and medical journals so that they become freely available to the public.

Support of the foundation is provided for by grants from other philanthropic foundations, industry, government agencies and private individuals. Foundations which have contributed to the advancement of the work of the laboratory since 1930 to the present time include the National Research Council, the Rockefeller Foundation, the National Academy of Sciences (Bache Fund), the American Academy of Arts and Sciences (Permanent Science Fund), the American Philosophical Society (Penrose Fund), Child Neurology Research, the Dazian Foundation for Medical Research, the Finney-Howell Cancer Research Foundation, the Josiah Macy Jr. Foundation, the Applied Research Foundation and the John Simon Guggenheim Memorial Foundation. Federal funds have been given both for cancer studies and for investigations of fatigue of airplane pilots. Contributions from industries in support of the fatigue investigations have been made by the Parker Manufacturing Company and the L. Farber Company, both of Worcester, the American Optical Company of Southbridge, the Schering Corporation of Bloomfield, New Jersey, and the G. D. Searle Company of Chicago, Illinois. The Searle Company has made extensive grants in support of a variety of the foundation's activities. Research work made possible by these industrial grants are published and thus made freely available to the public.

THE SOUTHERN BRANCH OF THE TEXAS ACADEMY OF SCIENCE

THE annual meeting of the Southern Branch of the Texas Academy of Science was held at Corpus Christi

Junior College on April 14, under the chairmanship of Dr. W. Armstrong Price, of Corpus Christi. Fifty-five persons registered for the meeting. Twenty papers were presented, covering a wide variety of scientific subjects from astronomy to zoology. In addition to Dr. Price, those who were active in organizing the meeting included Dr. Gordon Gunter, Institute of Marine Science, University of Texas, Rockport, and Dr. J. C. Cross, Texas College of Arts and Industries, Kingsville, who worked with the following committee on local arrangements: Professor John S. Kelley, of the department of chemistry, and Professor S. S. Wilks, of the department of biology, both of Corpus Christi Junior College; and Professor B. E. Schulze, of the department of science of the Senior High School.

The executive council of the academy was represented at the meeting by Dean W. R. Woolrich, of the School of Engineering of the University of Texas, and past president of the academy. The principal address was given by Dr. E. J. Lund, of the university, who spoke on a proposed new "Institute of Marine Science" on the Texas Gulf Coast.

The Program Committee was made up of Dr. J. C. Cross, chairman of the department of biology of the Texas College of Arts and Industries, Kingsville; Dr. W. Armstrong Price, of Corpus Christi; J. Sutton Myers, of the Soil Conservation Service, Raymondville; Mrs. L. Irby Davis, of the department of science, Senior High School, Harlingen; and Miss Velma Wilson, of the department of science, Junior College, Brownsville.

Officers elected for the coming year are, *President*, Professor S. W. Bass, Texas College of Arts and Industries, Kingsville; *Vice-president*, Professor J. S. Kelley, Corpus Christi Junior College; *Secretary-Treasurer*, Dr. Otto R. Nielsen, dean of the faculty of the Texas College of Arts and Industries.

THE VIRGINIA ACADEMY OF SCIENCE

For the first time since its organization twenty-three years ago, the Virginia Academy of Science held this year on May 11 a "skeleton" meeting attended primarily by officers, members of the council, chairmen of committees and sections, and those living close to the place of meeting, Richmond. In the morning, a joint meeting of the executive committee of the Virginia Social Science Association and council members of the academy was held to consider ways and means by which both organizations might work together for the welfare of the state. At the academy meeting in the afternoon, progress reports were made concerning the eighty active science clubs, the cooperation between the academy and the State Department of Education in eventually making it possible for pupils in the public-school system of Virginia to know more about local natural resources, the "machinery" set-up to make an inventory of the research facilities in state institutions and industrial laboratories, the plan to enroll in the academy more scientists from industry, the proposed Virginia Research Institute, the scholarships set aside by all the colleges of Virginia as awards in a Science Talent Search on a state level, the investigative work on local flora, the James River Monograph, the proposed State Science Museum and the endowment fund which now amounts to approximately $14,000. A resolution was adopted favoring the "Scientific and Technological Manpower Bill," H.R. 2827.

Dr. Robert F. Smart, in retiring as president, pointed out how effectively members of the academy had contributed to the welfare of Virginia during the past year by cooperating fully with various agencies of the State and Federal governments, the State Chamber of Commerce, the American Association for the Advancement of Science, the National Science Talent Search directors and educational institutions. H. R. Hanmer, director of research for the American Tobacco Company, was installed as president for the coming year. The following officers were elected by ballot: Dr. Arthur Bevan, State Geologist, *President-elect;* Dr. E. C. L. Miller, directing librarian at the Medical College of Virginia, *Secretary-Treasurer;* Dr. Sidney S. Negus, professor of chemistry at the Medical College of Virginia, *Assistant Secretary;* Dr. Gillie A. Larew, professor of mathematics, Randolph-Macon Woman's College, and Dr. Pearl M. Patterson, professor of biology, Hollins College, as new members of the council.

SCIENTIFIC NOTES AND NEWS

The Huxley Medal for 1945 has been conferred on Dr. A. L. Kroeber, professor of anthropology at the University of California at Berkeley, by the Council of the Royal Anthropological Institute of Great Britain and Ireland. Dr. Kroeber will deliver a lecture before the institute some time in November.

The Lister Medal for 1945, awarded in recognition of distinguished contributions to surgical science, has been presented to Professor Sir Howard W. Florey, F.R.S., of the University of Oxford, for his work on penicillin and its application. He will deliver the Lister Memorial Lecture, the date of which has not yet been announced.

The Patron's Medal of the Royal Geographical

Society, London, has been awarded to Sir Halford J. Mackinder, who was for twenty-five years professor of geography at the University of London, in recognition of "his eminent contributions to geography, including the first ascent of Mount Kenya in 1899, and his long and distinguished service in the advancement of the science."

IT is reported in the *Information Bulletin* of the Embassy of the U.S.S.R. that the Presidium of the Supreme Soviet of the U.S.S.R. has conferred upon Professor Peter Kapitza, member of the Academy of Sciences, the title of Hero of Socialist Labor, for his researches into the turbine methods of producing oxygen in his design of a turbine for the large-scale production of liquid oxygen. Another decree awards the Order of the Red Banner of Labor to the Institute of Physical Problems of the Academy of Sciences, of which Professor Kapitza is director.

ON the occasion of the tenth annual Hughlings Jackson Memorial Lecture of the Montreal Neurological Institute, delivered by Dr. Stanley Cobb, of the Harvard Medical School, a specially bound volume of the "Selected Writings of John Hughlings Jackson," edited by James Taylor, was presented to the lecturer. The subject of the lecture was "Neurocirculatory Asthenia."

DR. JOSEPH ERLANGER, professor of physiology at the School of Medicine of Washington University, St. Louis, has been awarded the certificate of merit and medal for distinguished service of the St. Louis Medical Society in recognition of "his contributions to fundamental knowledge of the cardiovascular and nervous system and to methods of physiological investigation, his excellence as a teacher and his devotion to the furtherance of medical research which have strengthened the hand and augmented the skill and discernment of present and future practitioners of medicine."

THE 1945 Eli Lilly and Company award in biological chemistry by the American Chemical Society to a chemist under thirty-five years was conferred on Dr. Max A. Lauffer, of the University of Pittsburgh.

THE Borden Company prize of $1,000 for research in the chemistry of milk of the American Chemical Society for 1945 has been awarded to Dr. Ben H. Nicolet, of the Bureau of Dairy Industry, U. S. Department of Agriculture, Beltsville, Md.

THE Philadelphia County Medical Society has conferred the 1944 annual Strittmatter award on Dr. J. Parsons Schaeffer, professor of anatomy at Jefferson Medical College. Dr. Schaeffer was the twenty-second recipient of the award, a gold medal and a scroll, presented in recognition of "his long and distinguished career as a teacher, author and scientist in the field of anatomy, and his sincere and untiring devotion and constructive efforts to safeguard high standards of medical research."

ON the occasion of its seventy-fifth commencement exercises on May 28, the Massachusetts State College, from which he was graduated forty years ago, conferred the honorary degree of doctor of science on Professor Richard L. Adams, of the department of farm management of the University of California.

DR. WILLIAM REED VEAZEY, of the Dow Chemical Company, has been elected president of the Electrochemical Society, Inc.

THE American Institute of Chemists, by mail ballot, has elected the following new councilors for three years with terms expiring in May, 1948: Dr. Norman A. Shepard, chemical director of the American Cyanamid Company, New York; Dr. W. D. Turner, assistant professor of chemical engineering at Columbia University, reelected, and Dr. James R. Withrow, professor and chairman of the department of chemical engineering of the Ohio State University.

AT the annual meeting on May 1 of the Royal Institution, London, Lord Rayleigh was elected *President;* Sir Robert Robertson, *Treasurer,* and Dr. A. O. Rankine, *Secretary.*

OFFICERS of the Chapter of Sigma Xi at Western Reserve University were elected on May 28 as follows: Dr. Helen A. Huncher, professor of home economics, *President;* Dr. Harry Goldblatt, professor of experimental pathology and associate director of the Institute of Pathology, *Vice-president;* Dr. Moffatt G. Boyce, associate professor of mathematics, *Secretary,* and Dr. A. Sidney Harris, assistant professor of physiology, *Treasurer.* At this meeting Dr. Robley C. Williams, professor of physics and astronomy at the University of Michigan, gave an address entitled "Three-Dimensional Electron Microscopy."

DR. GUSTAV A. L. MEHLQUIST, of the University of California at Los Angeles, has been appointed associate professor at Washington University, St. Louis, and a member of the horticultural staff of the Missouri Botanical Garden. He will continue his breeding work with carnations and delphiniums, representing an appreciable expansion in experimental horticulture at the garden. The appointment becomes effective on October 1. The experimental culture of orchids from seed carried out in the past few years by Dr. David C. Fairburn has necessitated the transfer of this branch of work to the arboretum ranges at Gray Summit, Mo., where large-scale techniques are more feasible. When Dr. Mehlquist takes up his work at the garden, Dr. Fairburn will become orchidologist in charge of the more than 20,000 plants at Gray Summit.

Dr. William W. Peter, associate professor of public health and chief of sanitary inspection in the department of health, Yale University School of Medicine, has become director of the training division of the Institute of Inter-American Affairs, Washington, D. C.

Dr. C. M. Child, professor emeritus of zoology at the University of Chicago, now in the School of Biological Sciences of Stanford University, has been invited to take part in the celebration of the two hundred and twentieth anniversary of the Academy of Sciences of the U.S.S.R. in Moscow and Leningrad from June 15 to 28, as guest of the academy.

Raymond E. Birch has been appointed director of research of the Harbison-Walker Refractories Company, with which he has been associated since 1930, to succeed the late Fred A. Harvey.

Dr. A. C. Thaysen, of the Chemical Research Laboratory of the Department of Scientific and Industrial Research of Great Britain, has been appointed director of the newly established Colonial Microbiological Research Institute in Trinidad for the general study of microbiological problems under tropical conditions. Dr. Thaysen has left for Trinidad to discuss there the problems of the institute. It is hoped that it will be possible to afford facilities for postgraduate work by visiting men of science in addition to the work of the staff.

Dr. George Calingaert, director of chemical research of the Ethyl Corporation, is at the request of the U. S. Army Air Corps now in Europe as an operations analyst for the United States Strategic Bombing Survey.

The resignation as of July 1 is announced of Dr. Marvin R. Thompson, president and director of the Warner Institute of Therapeutic Research, New York City.

Clifford E. Jurgensen, formerly chief psychologist of the Kimberley-Clark Corporation, has been appointed personnel director of the Minneapolis Gas Light Company. He took up this work on May 15.

The National Research Council has made a grant to Dr. Thurlo B. Thomas, of the laboratory of anatomy of the Medical Branch at Galveston of the University of Texas, for research on the action of alloxan.

Dr. Alexander Fleming, professor of bacteriology at the University of London and the St. Mary's Hospital Medical School, arrived in New York City on May 28, and left the following day for Washington. He plans to make a tour of hospitals and laboratories in the United States. On May 29 he gave a lecture on penicillin before the staff and students of the College of Physicians and Surgeons of Columbia University.

Dr. William J. Robbins, director of the New York Botanical Garden, writes to Science: "I have just received word that Professor Pierre Nobécourt, of the University of Grenoble, is in good health, that Grenoble suffered only minor war damage and that the University and Technical School are both intact."

B. J. Brent, of Roche Organon, Inc., writes to Science that he has "received news that Professor Ernst Laquer is all right and is living in Amsterdam as before the Nazi invasion. This is the first authentic information received about him in approximately five years. Professor S. E. De Jong and Dr. J. Freud are also well in Amsterdam, Holland."

The Kober Foundation lecture of the School of Medicine of Georgetown University was delivered on March 28 by Captain Lloyd R. Newhouser, M.C., on "The Role of Whole Blood Plasma and Plasma Fractions in War Medicine." Captain Newhouser was presented with an honorarium of $500 by Lawrence C. Gorman, S.J., president of Georgetown University. The selection of a lecturer was made this year by the Association of Military Surgeons of the United States.

At the May meeting sponsored jointly by the sections of the Electrochemical Society and of the American Chemical Society at Midland, Mich., Dr. Colin G. Fink, of Columbia University, spoke on "The Electrochemistry of the Rare Metals," referring in particular to his own researches.

Dr. John R. Murlin, Ross professor of physiology and director emeritus of the department of vital economics of the University of Rochester, delivered on May 16 the twenty-eighth Mellon Lecture of the Society for Biological Research of the School of Medicine of the University of Pittsburgh. His subject was "The Biological Value of Proteins in Relation to the Essential Amino Acids."

Speakers at the recent postgraduate session of the Army Air Force Regional Hospital, San Antonio Aviation Cadet Center, included Dr. René DuBos, of the Rockefeller Institute; Dean Tinsley Harrison, of the Southwestern Medical College, Dallas; Dean Chauncey D. Leake, of the Medical Branch at Galveston of the University of Texas, and Lieutenant Colonel Roy G. Grinker.

An address on "X-ray Analysis: Past, Present and Future" was given before the Royal Institution on May 11 by Sir Lawrence Bragg, F.R.S.

The American Society of Mechanical Engineers will hold an Aviation War Conference on June 11 to 14 at the University of California at Los Angeles. Speakers

in the four evening sessions will include well-known technical men in the aircraft industry. New aircraft techniques and a projection of post-war plans will be discussed in thirty-eight papers to be read at sixteen separate meetings. The conference is under the auspices of the Southern California Section of the society. Dr. Clarence A. Dykstra, provost of the University of California at Los Angeles, will address the opening session on Monday evening, June 11.

THE "Oliver Lodge Scholarship," with a basic annual value of £250 and tenable for one year, has been founded to commemorate the twenty-fifth jubilee of the radio section of the British Institution of Electrical Engineers.

IT is reported in *The Times,* London, that the University of Bristol, which already has chairs of mechanical, civil and electrical engineering, will establish a department of aeronautics in the faculty of engineering. This development is made possible by a gift of £60,000 by the Bristol Aeroplane Company for the establishment of the Sir George White Chair of Aeronautical Engineering, named in memory of the founder and first chairman of the company, who was one of the pioneers of British aviation.

DISCUSSION

A NOTE ON DR. NOVIKOFF'S ARTICLE

HAVING myself been for a long time deeply interested in the philosophy of organism and the theory of integrative levels in its application to the sciences, the appearance of Dr. Novikoff's article in SCIENCE for March 2, 1945, during the few weeks when I happen to be in the United States on my way back to Chungking, where I direct the Sino-British Science Cooperation Office, was for me a happy coincidence. It is a great pleasure to see this philosophy gaining ground, nearly twenty years after the pioneer work of J. H. Woodger, which found its expression in his "Biological Principles" (Kegan Paul, London, 1929).

Once we adopt the general picture of the universe as a series of levels of organization and complexity, each level having unique properties of structure and behavior, which, though depending on the properties of the constituent elements, appear only when these are combined into the higher whole, we see that there are qualitatively different laws holding good at each level. The phenomena of a higher level can not be understood without knowledge of the behavior of its constituents at the lower levels. Exactly how much light the lower-level phenomena throw on the higher-level phenomena at each stage, however, will probably long remain a matter involving differences of opinion. Thus Dr. Novikoff seems to take the view (p. 213) that the behavior of the lower animals, whether solitary or in primitive association (societies?) has little relevance to the phenomena of human society, while Gerard, as well as Emerson, on the contrary, have argued that the lower animals have much to teach us about the higher human level. On this point I should be inclined to agree with Dr. Gerard, who is, I am sure, not likely to fall into what I have elsewhere called "the heresy of biologism" ("Time, the Refreshing River," Macmillan, 1944), the fascist doctrine that unending internecine strife is as much the law of human society as it is of the wild forms of animal life. It would be a pity if, in the interests of maintaining the uniqueness of the human sociological level, we were to return to an almost ecclesiastical separation of man from the rest of the living world, without the consolation of an angelic world with which he might ally himself. This would hardly be in accord with the idea of scientific socialism.

Novikoff also takes Gerard to task for speaking of a "mysteriously operating 'organizing trend'" in the universe. Mysterious it may still be to us, as it was to Anaximander or to Lucretius, but it is undoubtedly there. For me it has never been possible to describe it otherwise than as an overall continuous rise in level of organization through cosmic, biological and social evolution. Perhaps Dr. Novikoff fears that a belief in this trend might lead to inaction in the social field. The United Nations, he says, do not rely on any evolutionary fatalism, but rather on armed might, actively applied, to defeat fascism and keep humanity on the road of progress. I have always felt that a helpful reflection here is that, although the general direction of process is known, the speed at which it goes on is not known, and depends directly on the activities of each one of us, thinking willing monads of the highest level. If a thousand years of human suffering more or less depend upon our actions here and now, we need hardly fear succumbing to fatalism when we recognize a universal trend in the world process.

I would like to add once again my appreciation of Dr. Novikoff's stimulating contribution to the discussion of this fundamental subject.

JOSEPH NEEDHAM
BRITISH SCIENTIFIC MISSION, CHUNGKING

EXTRAPOLATION FROM THE BIOLOGICAL TO THE SOCIAL

IN his article in SCIENCE,[1] Novikoff cuts a wide

[1] Alex B. Novikoff, SCIENCE, 101: 2618, 209–215, 1945.

critical swath, and we are among the frail straws cut down. His argument starts much on the same premises as ours, and ends by agreeing with many of our conclusions, but he finds our intervening course badly muddled and rather reprehensible. Gerard, especially, is accused of teleological and fatalistic views likely to give comfort to fascists and to sluggards. This is a novel experience to one often called a positivist and a mechanist.

We are grateful to Novikoff for bringing attention to our papers[2] and urge interested readers to refer to these more extended statements (and to Allee[3]), if they would discover what the shooting is about. Novikoff raises several valid queries. Mostly his answers and ours are in agreement; sometimes his criticisms are based on a misunderstanding of our position and occasionally are inconsistent with his own statements; and, finally, one or two real differences exist between us.

Novikoff emphasizes that: the part-whole relationship is reciprocal; atomism on the one hand and holism on the other are but parts of the truth; a new level of organization is attained by some integration of the simpler units but not by their mere summation; different mechanisms of interaction operate at different levels with unique laws, but that common attributes are encountered at the different levels (integration, individuality, evolutionary continuum, ontogeny, inheritance). We have been as emphatic on these points, yet Novikoff writes as if he were refuting us. Gerard,[4] as Novikoff, has emphasized the integral aspect of neural activity. Novikoff writes, "There is both continuity and discontinuity in the evolution of the universe; and consideration of one to the exclusion of the other acts to retard the development of biological and social sciences"; but then stresses the uniqueness of each level and upbraids us for emphasizing some similarities. Yet we have also dwelt upon distinctions, and he has recognized resemblances, both in attributes and causitive forces. But here is a real difference at last, for Novikoff seems, at the psychological-sociological level, to isolate completely everything human from the rest of nature and strenuously objects to our failure to do so.

We have argued that, since societies are living systems, they obey those most general laws which apply to all living systems. This says, for example, that social evolution and biological evolution are both subject to any statements applicable to "evolution," not that the two subclasses are identical. To recognize that growth of an individual, increase of a population, gene duplication and even, probably, learning are all subsumed under the concept of autocatalysis does not imply that the same detailed mechanism is involved in all cases.

The emergence of symbolic communication as a factor in evolution is no more dramatic than is the emergence of the rapid nerve impulse. It hardly justifies Novikoff's statement that "Progress in social development is basically different from progress in organic evolution. . . . Progress in organic evolution occurs without a set plan or direction; social progress rests upon planned activity of men." Has not, in fact, biological evolution exhibited a single direction, towards greater complexity and integration, as have inorganic and social evolution as well? Has a lion stalking his prey no "plan" and is his behavior without influence on organic evolution? Conversely, has social evolution been rationally planned over much of history; is it so even now to any great extent? Has natural selection played no role in shaping the appearance of human cooperation, which furthers man's adaptation in meeting such biological needs as nutrition, defense, reproduction and environmental control? Are we to be dubbed mystics for asking, concerning the human mind which makes man's integrated societies possible, how it came to be evolved—instead of asking only how it evolved?

The human mind, or eye, is understandable in terms of its function, as well as of its mechanism. Man can make sense of its appearance in nature, in each case, by noting what it does or, in evolutionary terms, what its adaptive significance is, how it aids its possessor. This is certainly teleological or "purposive" in a naturalistic sense. But it does not imply a "divine purpose in nature." And it in no way interferes with, but rather helps to raise, the mechanistic question—"How does this thing work, or develop?" The physiologist frequently thinks in terms of what would be useful to the body, of what job a mechanism might do, and so gets cues for his experimental search. Aquatic mammals could use special devices to enable them to remain long submerged; such were sought. The parathyroid hormone raises blood calcium, teleology suggests low blood calcium as an effective stimulus to parathyroid secretion. The basis of physiological regulation—a disturbance in equilibrium engenders a response tending to counteract that disturbance—is purposive in its effects, as is indeed the very concept of regulation. Mechanism and purpose are merely looking at sets of events from the two directions of the time axis. Looking backwards reveals mechanism; looking forwards, utility or purpose. Both are useful and supplement one another. Neither is to be fully understood without a knowledge of its development and evolution. Both imply uniformity (or period-

[2] Especially: R. Redfield (editor), "Biological Symposia" 8, 1942; R. W. Gerard, *Philos. of Science*, 9: 92–120, 1942.

[3] W. C. Allee, Science, 97: 517–525, 1943.

[4] R. W. Gerard, *Ohio Jour. Sci.*, 41: 160–172, 1941.

icity) and usefulness (or adaptation) in nature. Purpose, as we have used it, does *not* imply a sentient purposer.

Novikoff would reserve purpose to man, as a conscious volition, and so set him apart. Seeing purpose elsewhere, he says, is an anthropomorphism. And so it is, if conceived as conscious volition based upon symbolic learning. Indeed, so is seeing causation, related to man's feeling of volition in himself. Alas, so is everything man thinks, for he can think only as man. But if man's mind is itself a natural phenomenon, this is not too disheartening. For we see the mind evolving as part of the whole epic of evolution, and to be explained causally in terms of the body and its environment, just as life earlier evolved from the inanimate and is still tied to the laws of matter. To recognize that the known universe trends toward greater complexity is not to say that some intelligence has this as a deliberate purpose; and it is nonsense to state that such recognition leads to social inaction. (See Needham's accompanying note.) Our position seems to us far less mystical and more intellectually frank than to offer reason and purpose, as Novikoff does, as epiphenomena somehow uniquely acquired by man independently of any biological causation or evolutionary trend.

Novikoff quotes Emerson's statement that "the evolution of human social and ethical characteristics is governed by the same forces which have been directing organismic evolution through the ages," and then states that these "forces" are social in the human case, biological (mutation, etc.) in the other. But ethical systems help to integrate human society, as genetic systems do organisms, so that both have at least certain similarities of function. Further, both systems vary; favorable variations in either survive in relation to their function; and these variations are often inherited. Both systems thus evolve similarly under similar pressures; and these similarities are not "purely formal and therefore meaningless." Purely formal similarities are often very meaningful; on just such a basis, for example, the effect of myelin internodes in accelerating nerve conduction was predicted by Lillie from the behavior of an iron wire in an interrupted glass tube in nitric acid.

Biological evolution, on a genetic base, is indeed very different from social evolution based on transmitted symbols; but fundamental similarities might still allow some general predictions. The natural selection of whole integrated systems, for example, has led to an evolutionary increase in specialization and integration (cooperation) of the units composing individuals and superindividuals, both at the biological and the social levels. (And including the tapeworm, *contra* Novikoff.) Is it an unsound extrapolation to expect human social systems also to evolve toward greater cooperation? If two systems have both likenesses and differences, it is no argument against the likenesses to point out the differences. Novikoff, agreeing that "society will develop eventually to a high level of cooperation," still evidently thinks that the causes of similar evolutionary trends in societal and biological systems[5] have no basic identity.

True homologies (genetic similarities) are not to be expected between two different levels, as intracellular organelle and multicellular organ, or body organ and social institution. But analogies (functional similarities without genetic identity) may well exist, and are not all merely chance resemblances or euphonious metaphors. Convergent evolution of analogous functions between different organismic levels is well established, and inquiry into their origins and causes, far from being extrascientific, leads, for example, to clearer formulation of evolutionary pressures as of how the environment operates through natural selection.

We have also expressly recognized the dangers in analogical reasoning based on spurious or superficial resemblances in the presence of basic differences. Especially with phenomena in widely separated fields of knowledge, the scholar in one may go astray in the other. Also, rationalization from personal bias has often occurred.[6] Spencer certainly committed gross errors in detail, and it would be surprising if we did not. The less similar two systems, the more difficult is it to detect true resemblances; but, when these are discovered, the more important is the resulting insight likely to be. Nor is it of light importance that the tremendous accretion of physiological, zoological and sociological knowledge since Spencer's time permits more precise comparisons which dramatically substantiate earlier generalizations.

Which brings us, finally, to a genuine philosophical difference. We maintain that at each superposed level of integration new unexpected properties emerge, but that the new properties must be commensurate with the old; must fit in their general framework, not violate it. Novikoff disagrees with, shall we say, enthu-

[5] As we have used the terms, biological and societal, the impression might be given that they are parallel categories. There is a change in level from the so-called solitary individual to the social group, alike in insect and human. In both cases, a specialized society has developed from more primitive groups, of sex, family and other aggregations. The social level is one of the most evolved sublevels of living systems in the same sense as the biological level is of material systems. To restrict the term "social" to human groups, depending on symbolic interchange, and separate it sharply from "biological," which encompasses insect groups, is an arbitrary semantic decision on Novikoff's part.

[6] R. Hofstadter, "Special Darwinism in American Thought, 1860–1915," 191 pp. Philadelphia: University of Pennsylvania Press. 1944.

siasm, when he condemns, as a support for fascism, "the thesis that man's biology decides his social behavior." In his view, the laws and behavior of higher level systems are *by their nature* unpredictable from those of their lower level constituent systems, and presumably the reverse; in our view, they are not of necessity unpredictable. Emergent attributes are difficult to predict, to be sure, because man yet knows little; but every significant scientific experiment is an act of faith or confidence in the ultimate understandability and predictability of nature. And this is not atomism, for it works both ways—the brain could never be fully understood without knowing mind, nor the mind without knowing brain. Where Novikoff would say that man's affairs are sharply separable into the sociological or the biological and that blurring the distinction is dangerous, we say they are part of each and that blurring the similarity is also dangerous. We recall that Darwin's clue for the concept of biological evolution came from sociological considerations and that his concept was, in turn, the stimulus to fruitful sociological thought.

Fortunately for our main theme, whether the particular mechanisms of evolution are alike or different at cellular, organismic or societal levels, comparable qualities repeatedly emerge. It remains true that the fact of evolution applies to all the universe we know—inanimate, living, thinking—and that its overall trend is consistently towards greater differentiation by specialization of units combined with greater integration (interaction or cooperation) of units in the whole.

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THE COLORATION GIVEN BY VITAMIN A AND OTHER POLYENES ON ACID EARTHS

IN one of the recent issues of SCIENCE, A. Lowman[1] reported on the blue coloration which appears if vitamin A, which is dissolved in a non-polar solvent, is brought into contact with the commercial adsorbent, Super Filtrol. His observations were confirmed by H. R. Kreider.[2]

Evidently because of the prevailing difficulties in obtaining foreign literature, neither of the authors mentioned seems to be aware of the fact that this interesting reaction has been observed and interpreted by P. Meunier[3] three years ago. According to Meunier's explanation, some acid earths which possess incomplete electronic octets are able to give rise to an intensely blue color when they are in contact with vitamin A which is dissolved in a non-polar solvent; by donating unshared electrons to such adsorbents, the vitamin molecule undergoes polarization and forms positively charged, strongly resonating structures. A few very debatable points in Meunier's interpretations shall not be discussed here; for example, the alleged restriction of the resonating system to twice four double bonds in the β-carotene molecule.

The Carr-Price reaction and some color tests given by sterols have also been treated by Meunier and his collaborators.[4]

Of course, the coloration on acid earths can not be expected to be specific for vitamin A. In fact, carotenoids were mentioned by Meunier and the reaction was observed by Lowman to be given by carotene.

A similar coloration is also shown by a new polyene, now under investigation, which is widespread in plants, shows intense fluorescence in ultraviolet light and was recently reported in collaboration with A. Polgár.[5] We find that if a highly purified, colorless petroleum ether solution of e.g. 0.01 mg of this compound is placed in contact with filtrols, the solid phase turns azure blue. The formation of this color is irreversible in the sense that an alcohol or acetone eluate, after transfer into petroleum ether, does not show the typical extinction maxima of the starting material (331, *348*, 367 mμ) as represented in a published curve.[5]

A deep coloration on acid earths, *e.g.*, on purified Super Filtrol can also be obtained with a benzene solution of diphenyloctatetraene, $C_6H_5(CH{=}CH)_4 \cdot C_6H_5$, under suitable conditions.

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ANAEROBIC RESPIRATION VS. FERMENTATION

THE terms fermentation and anaerobic respiration have justifiably been put under the microscope in two recent discussions in SCIENCE.

Seifriz[1] objects to the use of the term fermentation for anaerobic respiration when the reactions involved are substitutes for energy-yielding anaerobic processes necessary for life.

The criticism seems a valid one, for the word fermentation as used historically by Pasteur *et al.* and, as used currently, does not denote the part which oxygen may or may not play in the reactions. In the literature, reference is repeatedly made to "alcoholic fermentation" and "acetic acid fermentation." The

[1] A. Lowman, SCIENCE, 101: 183, 1945.
[2] H. R. Kreider, *ibid.*, 101: 377, 1945.
[3] P. Meunier, *Comptes rendus de l'Acad. Franç.*, 215: 470, 1942.

[4] P. Meunier, R. Dulou and A. Vinet, *Compt. rend.*, 216: 907, 1943; P. Meunier, R. Dulou and A. Vinet, *Bull. soc. chim. biol.*, 25: 371, 1943; P. Meunier and Y. Raoul, *ibid.*, 25: 173, 1943.
[5] L. Zechmeister and A. Polgár, SCIENCE, 100: 317, 1944.

[1] William Seifriz, SCIENCE, 101: 88–89, 1945.

former occurs in the absence of oxygen and in the latter oxygen is involved. Hence, the term does not differentiate the intimate role of oxygen.

Goddard,[2] on the other hand, believes we would do well to retain the word fermentation for reactions involving the degradation of an organic molecule into two or more simpler molecules by an oxidation and reduction occurring within the original molecule or its products. He points out that, if the term anaerobic respiration is used according to its usual meaning (*i.e.,* in the absence of oxygen), in many types of tissues, *e.g.,* some tumors, contracting muscles, certain yeasts and some seeds, carbohydrate degradation occurs without the intervention of oxygen, even though oxygen may be present.

Hence, the word anaerobic respiration, like the word fermentation, in itself does not give an accurate picture of the actual type of respiration prevailing. Therefore, these two words which seem to be competing in scientific usage both fail because of the same ills.

In my opinion, the opposing views can be resolved into satisfactory agreement which will banish confusion in the minds of students of biochemistry and others, and we can still retain the word anaerobic respiration in popular usage as it is at present. We need simply to qualify the term to mean the state of respiration or the release of energy from a substrate in the cell, in which oxygen is *not one of the reactants,* whether or not it is present. Therefore, anaerobic respiration may prevail either in the presence or absence of oxygen, but in either case oxygen is not the hydrogen acceptor.

Aerobic respiration on the other hand refers to the active participation of oxygen in the energy-yielding process.

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PLEA FOR PUBLICATIONS

WE, in Belgium, have been deprived of American publications since the beginning of the war; accordingly, we have not been able to refer to published works in which we should be particularly interested. At the suggestion of my friend and former coworker at this institute, Major R. Roseman, Sn.C., of the American Army, I am addressing an earnest plea to the readers of SCIENCE for any available reprints on the following subjects: proteins, bilirubin, clinical and experimental studies on burns and penicillin. Any information whatever furnished along these lines would be greatly appreciated.

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SCIENTIFIC BOOKS

COMMERCIAL ANALYSIS

Commercial Methods of Analysis. By FOSTER DEE SNELL and FRANK M. BIFFEN. vii + 753 pp. Illustrated. 13.5 × 21 cm. New York: McGraw-Hill Book Company, Inc. 1944. $6.00.

THE authors state in the preface that this book is for the student who has already become familiar with the tools of quantitative analysis and the routine methods, and who desires further training in this field by a study of commercial methods and may serve as a manual to the industrial analyst. The first eighty pages are devoted to elementary subject-matter such as a description of the tools of the analyst; beakers, flasks, burettes and filter paper, and a discussion of such general operations as drying, weighing and extraction. Thirty pages deal with inorganic qualitative micro analysis.

The balance of the text is given over to procedures for the quantitative analysis of many industrial materials, including minerals, water, cement, ferrous, aluminum, and copper-base alloys, fats, soap, greases, solvents, paint, rubber, coal, gas, paper, sugar and some others. Little theory is presented; hence, the book, if it has any pedagogical value, will be more useful in the training of chemical analysts than in the education of analytical chemists. Standard methods are drawn from those published by the American Society for Testing Materials, the Association of Official Agricultural Chemists and others. Frequent deviation from official and recommended procedures are given, but seldom are these departures indicated as such.

The value of this book as a reference work is greatly lessened by the almost complete absence of literature citations. The reviewer could locate no more than eighteen specific citations in footnotes together with a few general references within the text of the book.

In spite of these faults, this book will properly find its place on the shelves of technical libraries and on the desks of many chemical analysts. It will serve as a point of departure when the latter are called upon to perform analyses which fall outside the routine of their day-by-day experience.

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[2] David R. Goddard, SCIENCE, 101: 352–353, 1945.

SYNTHETIC RUBBER

Synthetic Rubber from Alcohol. A survey based on the Russian literature by Anselm Talalay and Michel Magat. 298 pp. New York, N. Y.: Interscience Publishers. 1945. $5.00.

The first part of this book is a description of the Lebedev process which has been developed and used in Russia for the manufacture of butadiene from ethyl alcohol. In contradistinction with the multi-stage Carbide and Carbon process utilized in this country, the Lebedev process is a one-step catalytic process technologically simpler but yielding a large variety of by-products which have to be separated from butadiene before polymerization. Technical data on the rectification of the unconverted ethyl alcohol, on the absorption, desorption and distillation of the crude butadiene, on the separation and utilization of the by-products is given with some details in Chapters I and II.

The second part of the book is a well-integrated exposé of the present theories of polymerization phenomena and of physicochemical measurements of polymer properties. The authors very wisely did not confine themselves to the sodium polycondensation of butadiene, which is, according to the literature, the only process used by the Russians in the manufacture of synthetic rubber from butadiene; they present one of the best general treatments of the various polymerization techniques to be found in the literature. They have classified the abundant physicochemical data of the Russian investigators and frequently interpreted them in the light of recent theoretical concepts. They have also compared, when data were available, physical characteristics of sodium polybutadienes with that of emulsion polybutadienes and natural rubbers.

If the sole purpose of the authors was to make available, in a comprehensive form, the abundant literature published in Russia on the subject, they have fully succeeded in their task. As such, the book will be found very helpful to those interested in the field of polymerization.

From a general point of view this book is a war casualty of censorship and withholding of information. Examination of the bibliography shows how very little information has been published in Russian journals since 1936. It is the feeling of the reader that for one reason or another much pertinent scientific information has been omitted, thus rendering the treatment sometimes incomplete and occasionally scientifically meaningless. As a flagrant example, catalysts used in the Lebedev process are identified as a mixture of catalysts A and B with c and d as promoters. There is no indication as to what is the specific identity of catalysts A, B, c and d; whether the catalyst mixtures were identified by A, B, c, d in the Russian literature is not clarified, surprisingly enough considering how much other detailed information is given. The yield of butadiene, the nature of the by-products, the actual operational conditions are an intimate function of the specific nature of the catalysts used. Many graphs, tables and considerations in Chapter I lose most of their meaning, since they are not related to specific catalysts. The publishers must undoubtedly realize that the withholding of such information markedly decreases the value and therefore the saleability of the book.

To summarize, the quality of the book is uneven; Chapter III on polymerizations is by far the best; the book as a whole is an excellent survey of the Russian literature on the subject.

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SPECIAL ARTICLES

THE MECHANISM OF THE VIRUCIDAL ACTION OF ASCORBIC ACID[1]

The virucidal activity of ascorbic acid has been reported against vaccina virus[2] and poliomyelitis.[3] Knight and Miller[4] have recently demonstrated the virucidal activity of this compound against influenza A virus. We have confirmed the virucidal action of ascorbic acid against influenza A virus and will report our results indicating the mechanism of action of this compound.

Barron, DeMeio and Klemperer[5] have shown that the oxidation of ascorbic acid in air is catalyzed by Cu and they postulated that H_2O_2 is formed during the reaction. In the presence of 0.0002 mM of $CuCl_2$, pH 6.95, the half oxidation of ascorbic acid occurred in 10.3 minutes. These workers did not demonstrate the actual presence of H_2O_2, which they indicated was difficult because of its rapid decomposition into water and oxygen. Lyman, Schultze and King[6] have reported that their qualitative tests indicated the presence of H_2O_2 during the Cu catalyzed oxidation of ascorbic acid in air.

If H_2O_2 is the active virucidal agent, then catalase, which acts specifically upon H_2O_2, should completely abolish the activity of ascorbic acid. It should also be possible to show that H_2O_2 itself, in concentrations

[1] This investigation has been aided by a grant from the Josiah Macy Jr. Foundation.

[2] I. J. Kligler and H. Bernkopf, *Nature*, 139: 965, 1937.

[3] C. W. Jungeblut, *Jour. Exp. Med.*, 62: 517, 1935.

[4] C. A. Knight and W. M. Stanley, *Jour. Exp. Med.*, 79: 291, 1944.

[5] E. S. G. Barron, R. H. DeMeio and F. Klemperer, *Jour. Biol. Chem.*, 112: 625, 1936.

[6] C. H. Lyman, M. O. Schultze and C. S. King, *Jour. Biol. Chem.*, 118: 757, 1937.

approximating that theoretically produced by the oxidation of ascorbic acid at pH 7, inactivates influenza A virus.

Materials and Methods

Ascorbic acid: 1-ascorbic acid (Eastman) was freshly prepared before each titration. Solutions were adjusted to pH 7 and diluted in M/10 phosphate buffer.

Hydrogen peroxide: Merck, Superoxol (30 per cent. H_2O_2) diluted in M/10 phosphate buffer.

Catalase: Blood (rabbit) catalase, water clear[7] was kindly supplied by Dr. M. G. Sevag of this department.

Virus: The PR8 strain of influenza A virus was grown in the allantoic cavity of 10-day-old chick embryos. The test virus consisted of allantoic fluid diluted in buffered saline pH 7, and containing either 100 or 10 MLD of virus. Tests for viral activity were performed by instilling 0.05 ml of fluid intranasally into lightly etherized mice. The mice were observed for 10 days and death with typical lobar consolidation was recorded as D_6D_8, etc., *i.e.*, death occurred on the sixth or eighth day following inoculation. Mice surviving 10 days were killed and the extent of lung lesions reported as 0 (normal), 1^+, 2^+, 3^+, 4^+.

Experimental

The virucidal action of ascorbic acid and its neutralization by catalase: One ml of a 0.05M solution of ascorbic acid was added to 1 ml of influenza A virus solution containing 100 or 10 MLD; 0.5 ml of buffered saline was added to the solution to make a total volume of 2.5 ml. After remaining at room temperature for 10 minutes, 0.05 ml of the solution was inoculated into mice. The mice were observed for 10 days and the presence of virus reported as indicated under Methods. A 0.05 M solution of ascorbic acid is close to the minimal virucidal concentration since it causes only partial inactivation of a test solution containing 100 MLD of virus with complete inactivation occurring only in a solution containing 10 MLD (Table 1).

TABLE 1

THE VIRUCIDAL ACTION OF ASCORBIC ACID UPON INFLUENZA A VIRUS AND ITS NEUTRALIZATION BY CATALASE

Action of Ascorbic Acid	Neutralization by Catalase	Virus Control	Catalase Control	Catalase and Ascorbic Acid Control	Catalase and Virus Control
1 ml of 0.05M ascorbic acid, 1 ml of influenza A virus, 100 MLD (A) and 10 MLD (B). 0.5 ml buffered saline	1 ml of influenza A virus of 100 MLD (A) and 10 MLD (B). 0.5 ml catalase (1:10). 1 ml 0.05M ascorbic acid.	1 ml influenza A virus 100 MLD (A) and 10 MLD (B) 1.5 ml buffered saline.	0.5 ml catalase (1:10). 2 ml buffered saline.	1 ml catalase (1:10). 1 ml 0.05M ascorbic acid. 0.5 ml buffered saline.	1 ml virus 10 MLD. 1 ml catalase (1:10). 0.5 ml buffered saline.
A. (100 MLD of virus)					
D_7, D_{10}, 3 +, 3 +, 2 +, 2 +, 1 +, 1 +, 0, 0	D_6, D_6, D_6, D_6, D_7, D_7, D_8, D_8	D_6, D_6, D_7, D_8, D_8	0, 0, 0, 0	0, 0, 0, 0	D_7, D_7, D_7, D
B. (10 MLD of virus)					
0, 0, 0, 0, 0, 0, 0, 0	D_7, D_7, D_7, D_7, D_8, D_9, 2 +	D_7, D_7, D_8, D_8, 3 +			
Substituting 0.1% H_2O_2 for 0.05M ascorbic acid					
0, 0, 0, 0, 0	D_7, D_7, D_7, D_8, D_8				

In order to determine the inhibitory action of catalase 1 ml of virus was added to 0.5 ml of catalase diluted 1:10; 1 ml of 0.05 M ascorbic acid was then added and after 10 minutes at room temperature 0.05 ml of the solution was inoculated into mice. The results in Table 1 show that catalase completely neutralized the action of ascorbic acid.

Action of hydrogen peroxide upon influenza A virus: Hoagland, Ward, Smadel and Rivers[8] have shown that Cu is present in high concentration in their purified preparations of vaccinia virus. Though quantitative data are not available on the presence of Cu in influenza A virus it is reasonable to assume that Cu is present, since it is a normal constituent of living cells and exists in relatively high concentration in the chick embryo, the host for the growth of our strain of influenza virus. Assuming the presence of Cu in amounts as small as 0.0002 mM then at pH 7 half oxidation of ascorbic acid occurs in 10.3 minutes (4). At room temperature the theoretical yield of H_2O_2 from 0.05 M ascorbic acid would be 0.085 per cent.; in the presence of 0.01 mM of Cu the H_2O_2 formed would be approximately 0.14 per cent.

We have found the minimal concentration of H_2O_2 causing complete inactivation of 10 MLD of influenza A virus is 0.1 per cent. (Table 1). Therefore the virucidal activity of a 0.1 per cent. solution of H_2O_2 approximates the virucidal activity of the H_2O_2 re

[7] M. G. Sevag and L. Maiweg, *Biochem. Z.*, 288: 41, 1936.

[8] C. L. Hoagland, S. M. Ward, J. E. Smadel and T. M. Rivers, *Jour. Exp. Med.*, 74: 69, 1941.

lting from the Cu catalyzed oxidation of 0.05 M orbic acid.

Discussion

The role of Cu in the virucidal action of ascorbic id is still not clearly defined, though our preliminary servations have indicated that KCN inhibits the rucidal action of ascorbic acid presumably by combing with Cu to form a stable compound.

It is of interest to note that the bactericidal activity Penicillin B has also been reported as being due the production of H_2O_2. The Penicillin B was und to be a glucose oxidase producing H_2O_2 in the esence of glucose and oxygen.[9]

Summary

The theoretical yield of H_2O_2 formed during the idation of a virucidal solution of ascorbic acid approximates the virucidal action of an equivalent ount of H_2O_2. Both the action of ascorbic acid d H_2O_2 are completely neutralized by catalase. e action of ascorbic acid against influence A virus y therefore be explained as being due to the H_2O_2 rmed during the Cu catalyzed oxidation of ascorbic id.

The observed *in vitro* virucidal activity of ascorbic id obviously can not be utilized therapeutically bese of the presence of catalase in body tissues.

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BLOOD, URINE AND FECAL LEVELS OF STREPTOMYCIN IN THE TREATMENT OF HUMAN INFECTIONS OF E. TYPHOSA[1,2,3]

The clinical studies of the effect of streptomycin the course of typhoid infections in humans will be ported by Reimann, Elias and Price.[4]

The potency assay of streptomycin depends on a linder-plate technique, similar to the method used penicillin assay, in which a strain of *B. subtilis* was bstituted for *S. aureus*.[5] This procedure is also e that used in the assay of streptothricein.[6]

During this investigation, patients were given streptomycin in dosages ranging from one million to four million units daily. The drug was given by the intramuscular or intravenous routes and, in one patient, by the oral route which, on discontinuance, was followed by injection, using the intravenous drip method. Intramuscular and oral doses were given at three-hour intervals.

Blood and serum samples were usually collected after the first dose at intervals of 1, 2, 3, 6, 12, 24, 36, 48, etc., hours of treatment. Samples were also drawn at short intervals on discontinuance of dosage. Urine samples were collected at a number of short intervals following the initial dose and again on discontinuance of dosage. In the interim, 24-hour urine collections were made to determine the amounts of streptomycin present. In two cases fecal samples were assayed, when possible, on the basis of 24-hour collections.

Intramuscular and Intravenous Dosage

These routes of administration produced similar blood and serum levels in direct proportion to dosage. Four million units daily, given intravenously, resulted in whole blood levels with a mean of 12 units per ml and a mean of 28 units per ml of serum. Peak levels were reached within a few hours after the start and disappeared within 24 hours after cessation of dosage.

With an intramuscular administration of 20 million units over six days, 44 per cent. of the streptomycin was recovered in the urine. Following the intravenous dosage of 28 million units over 7 days, 70 per cent. of the streptomycin was accounted for in the urine. Urinary excretion appeared within $1\frac{1}{2}$ hours, with only traces remaining 72 hours after cessation of dosage.

Fecal levels were not determined with intramuscular dosage, nor were total recoveries determined by intravenous administration. However, four million units daily, by the intravenous route, produced from 100 to 130 units per gram of feces.

Oral Dosage Followed by Intravenous Administration

Four million units daily, by oral ingestion, produced no demonstrable blood level. Approximately 1 per cent. appeared in the urine, while at least 64 per cent. was eliminated in the stools over the period of oral dosage, with as high as 21,700 units per gram of fresh feces.

When oral administration was suddenly changed to intravenous injection, streptomycin promptly appeared in the blood and serum at levels comparable

[9] O. Schales, *Arch. Biochem.*, 2: 487, 1943.

[1] The method for the assay of streptomycin in citrated od, hemolysed with saponin, and urine was obtained ough the courtesy of Dr. J. M. Carlisle and Dr. D. F. bertson, of the Merck Institute for Therapeutic Rerch, Rahway, N. J.

[2] This work was conducted in the laboratory of Dr. A. Reimann in Jefferson Medical College, Philadelphia,

[3] Detailed methods of procedure will be presented in bsequent publication.

[4] H. A. Reimann, W. F. Elias and A. H. Price, *Jour. Med. Asn.*, in press.

[5] H. J. Robinson and D. G. Smith, *Jour. Pharmacol. and Therap.*, in press.

[6] J. W. Foster and H. B. Woodruff, *Jour. Bact.*, 45: 408, 1943.

to those observed previously, 65 per cent. was excreted in the urine and only 2 per cent. in the feces.

Table I presents representative data of streptomycin recoveries after various methods of administration.

The general impression prevailed throughout these tests that streptomycin in water solution, and in its passage through the body, was extremely stable, and it is very probable that recoveries in the urine and feces were actually greater than reported here. In this connection it is certain that total daily yields of urine and feces were not obtained because of uncontrolled eliminations by these very ill patients.

RESISTANCE TESTS

Robinson, Smith and Graessle,[7] employing the agar plate technique, reported that the growth of *Eberthella typhosa* was inhibited by one unit of streptomycin.

The streptomycin resistance of the typhoid organism, isolated from blood and stool cultures during this investigation, was measured by a broth culture technique in which 5 ml volumes of broth contained 1,000 organisms per ml, and concentrations of streptomycin ranging from 0.5 unit to 20 units per ml. Readings were made 24 and 96 hours after incubation at 37° C.

Three cultures from three patients, including two from stools and one from blood, isolated prior to streptomycin therapy, were all killed by 6 units, but not by 4 units, of streptomycin per ml of broth.

A culture, isolated from blood after nine days' intramuscular dosage of one million units/24 hours, showed no change in resistance.

A stool culture, isolated after a total oral dosag of 15 million units and a subsequent 8 million uni administered intravenously, likewise demonstrated n change in resistance.

Modification of the procedure, in which Wida negative human serum was added to the broth to a concentration of 10 per cent., did not materiall change the activity of streptomycin to all the abov cultures.

A control, consisting of a stock culture of *Eberthella typhosa* maintained for several years on ag culture, was killed by 2 units, but not by 1 uni of streptomycin in broth and serum-broth.

In connection with the similarity in resistan among the cultures isolated during this investigatio it is of considerable interest that positive isolatio were made in two persons whose stools contained 4 units per gram and 145 units per ml. Bearing i mind the enormous dosages administered, in contra to the *in vitro* resistance, it is possible that som inhibitory substance to streptomycin exists in th human body. Because of the considerable recoveri streptomycin was not destroyed by this agent, b its activity was very much reduced.

TABLE 1

STREPTOMYCIN LEVELS IN BLOOD, SERUM, URINE AND FECES AFTER VARIOUS ROUTES OF ADMINISTRATION

Patient	Interval dosage in units	Route	Blood† units/ml	Serum† units/ml	Urine levels: Volume	Units/ml	Interval recovery in units	Per cent. recovery based on interval dosage	Fecal level*: Fresh weight	Units/gram	Interval recovery	Per cent recovery based on interval dosage
								per cent.				per cent.
H	2 million	intra-muscular	5 to 7	13 to 14	2,580 ml	225	581,000	29	....	....	....	....
	4 "	"		15 to 20	2,200	640	1.4 million	32	....	....	....	....
M	4 million	intra-venous	12 (Mean)	27 (Mean)	3,100	1,000	3.1 million	77	....	....	....	....
	2 "	"	5 to 6	13 to 14	2,920	470	1.37 "	68	....	....	....	....
	24 hours after cessation of dosage				500	290	145,000		58.3 grams	40	2,330	
F	1 million	oral	none	none	2,200	4	8,800	0.9	181 grams	4,000	724,000	72
	2 "	"	"	"	1,900	12	22,800	1.1	732 grams (enema)	3,000	2.2 million	110
	4 "	"	"	"	1,300	29	38,000	0.95	113 grams	8,400	923,000	23
	2 "	intra-venous	6	19	3,200	330	1.06 million	53	180 ml (enema)	145 u/ml	26,100	0.7
	4 "	"	15	32	3,500	740	2.6 "	65	231 grams	220	51,000	1.3

* Fecal recoveries varied considerably from day to day, but over-all recoveries amounted to at least 64 per cent. by o dosage and approximately 1 to 2 per cent. by intravenous administration.
† These values are representative of the blood and serum levels existing at 12-hour intervals after initiation of dos

CONCLUSIONS

(1) Streptomycin levels in blood, serum, urine a feces were easily determined.

(2) Intramuscular and intravenous dosages w comparable with respect to demonstrable blood lev high urine recovery and, in intravenous dosage, a l fecal recovery.

(3) Oral administration produced no demonstra blood level, a very low urinary recovery, but an e tremely high fecal content. This is indicative t

[7] H. J. Robinson, D. G. Smith and O. E. Graessle, *Proc. Soc. Exp. Biol. and Med.*, 57: 226, 1944.

streptomycin, under the conditions of these investigations, was not readily absorbed through the intestines.

(4) The *in vitro* streptomycin resistance of cultures, isolated during therapy, did not differ from cultures isolated from blood and stools prior to the administration of streptomycin.

(5) The contrast between the very large dosages coupled with blood and fecal isolations during therapy, and the comparatively low *in vitro* resistance of these cultures, indicated the possible presence in the body of a substance inhibitory to streptomycin.

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PARA-AMINOBENZOIC ACID—ITS EFFECTIVENESS IN SPOTTED FEVER IN GUINEA PIGS[1]

IN contrast with the spectacular successes achieved by chemotherapy in bacterial infections, chemotherapy in viral and rickettsial diseases is in general non-effective. This applies particularly to the sulfonamide agents. Greiff and Pinkerton[2] have shown that sulfanilamide does not inhibit rickettsial growth in egg yolk-sac. Still more striking are the observations by Snyder, Maier and Anderson[3] that the sulfonamide drugs have a deleterious effect in experimental typhus. These phenomena, which offer another evidence of the apparently different metabolic requirements and activities of the intracellular rickettsiae, led Greiff, Pinkerton and Moragues[4] to the use of "enzyme activators" in rickettsial infections. The inhibitory action of p-aminobenzoic acid (PABA) on rickettsial growth was observed in egg yolk-sacs infected with murine typhus rickettsiae. A favorable effect of this drug on murine typhus infection in mice was also reported.[4] The beneficial effect of PABA on the clinical course of louse-borne typhus in man was established by the United States of America Typhus Commission unit in Egypt.[5]

On the basis of these observations PABA was tested by us in guinea pigs infected with Rocky Mountain spotted fever. The strain of tick origin (Rocky Mountain Laboratory) proved highly virulent to guinea pigs: the regular 72 hours' incubation period is followed invariably by high fever of 5 to 8 days' duration. The death-rate in infected guinea pigs is 100 per cent.

The present work was directed into the possible protection of animals against the disease by the use of PABA. For this purpose guinea pigs were given the drug in proportion of 2 gm of the powder per each 100 gm of high protein feed *ad lib.* The administration of this mixture was started shortly after the intra-abdominal injection of the infective material (spleen or blood). In other series the drug was given 24 hours prior to the infection or 24, 48 and 72 hours thereafter. The daily PABA treatment was then continued for 7 to 10 days, after which time it was withdrawn.

As compared with the clear-cut febrile and fatal disease in control animals a striking change in the response of test guinea pigs was observed. Out of 12 guinea pigs in which PABA intake preceded the injection by 24 hours three animals showed fevers of 1 to 3 days' duration; two guinea pigs reacted with slight and late elevations for 1–2 days, while seven animals remained completely afebrile. Two deaths were recorded. In another series of 17 guinea pigs treated with PABA beginning with the day of spotted fever injection, eleven animals remained afebrile during two weeks' observation, three reacted with one or two days' fever, two developed typical spotted fever and died, while one died showing no fever. As a whole, in 80 per cent. of test guinea pigs the fever was either entirely absent or reduced to abortive mild attacks.

When PABA was administered during the incubation period 30 per cent. of guinea pigs remained afebrile even when the drug was given 72 hours after injection. However, the animals of this series showed a rather erratic appetite, resulting in an inefficient intake of PABA.

These facts indicate that PABA, given before or shortly after infection, can prevent the appearance of clinical manifestations of the fatal spotted fever. In the large majority of test animals the visible symptoms (fever and scrotal reaction) were entirely absent. Nevertheless, some afebrile guinea pigs showed pathological lesions (splenomegaly, pneumonitis) typical for spotted fever. When the spleen was injected into normal guinea pigs the latter reacted with typical spotted fever like the controls. The surviving afebrile animals were then reinoculated with spotted fever rickettsiae and showed complete immunity. It seems, therefore, that the absence or mildness of clinical symptoms indicate rather a suppressive than destructive effect of p-aminobenzoic acid on spotted fever rickettsaie with the result of

[1] Study assisted by a grant from the American Foundation of Tropical Medicine, Incorporated.

[2] D. Greiff and H. Pinkerton, *Proc. Soc. Exp. Biol. and Med.*, 55: 116–119, 1944.

[3] J. C. Snyder, J. Maier and C. R. Anderson, Report to the Division of Med. Sciences, Nat. Res. Counc., December 26, 1942.

[4] D. Greiff, H. Pinkerton and V. Moragues, *Jour. Exp. Med.*, 80: 561–574, 1944.

[5] A. Yeomans, J. C. Snyder, E. S. Murray, C. J. D. Zarafonetis and R. S. Ecke, *Jour. Am. Med. Asn.*, 126: 349–356, 1944.

inapparent (subclinical) infection. This phase of biochemical activity is associated with or followed by immune phenomena by which the guinea pig acquires active resistance to subsequent infection.

The present study still in progress extends the previously observed effectiveness of p-aminobenzoic acid in other, milder rickettsioses[4,5] and proves its protective value in the highly virulent spotted fever.

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STUDIES ON THE MECHANISM OF ANTIBACTERIAL ACTION OF 2-METHYL-1,4-NAPHTHOQUINONE[1]

THE antibacterial activity of quinones has been recognized since 1911.[2,3,4,5,6,7] Interest in this phase of their activity has been stimulated in recent years by the discovery of the quinone structure in antibiotics derived from molds.[7,8] Synthetic 2-methyl-1,4-naphthoquinone as tested in this laboratory has been shown to be bacteriostatic and bactericidal for both gram-positive cocci and gram-negative bacilli, and a similar effect has been noted on many species of fungi. It was found that minimum effective bacteriostatic and bactericidal concentrations for *Escherichia coli* in a chemically defined medium were lower than in the usual peptone broth or agar (0.00125 per cent. to 0.0025 per cent. instead of 0.005 per cent. to 0.02 per cent.); also that in Brewer's thioglycolate medium, both bacteriostatic and bactericidal activity of concentrations as high as 0.04 per cent. were nullified in freshly prepared medium, although in medium prepared some three months previously and thoroughly shaken immediately before use, minimum effective bacteriostatic and bactericidal concentrations were approximately the same as in other peptone media. The effect of the fresh Brewer's medium did not appear to be due to its anaerobic properties, since tests on agar plates incubated in an anaerobic jar gave the same endpoints as those obtained on aerobic incubation. The following work was undertaken in an attempt to explain this behavior.

METHODS

The medium used was McCleod's synthetic medium,[9] with asparagin and $(NH_4)_2SO_4$ as sources of nitrogen, glucose, NaCl, phosphates and traces of Fe, Ca and Mg, dispensed in 8″ by 1″ test-tubes in accurately measured amounts.

The quinones employed included 2-methyl-1,4-naphthoquinone; the water-soluble sodium bisulfite addition product of 2-methyl-1,4-naphthoquinone; 2-methyl-3-methoxy-1,4-naphthoquinone, 2-methyl-3-chloro-1,4-naphthoquinone and 2,6-dimethyl-1,4-naphthoquinone, all pure synthetic compounds prepared in the chemistry research laboratories of this corporation. Solutions were made up aseptically in acetone or water, depending on their solubilities, in concentrations 25 times as strong as the highest final concentration desired in the medium. Serial dilutions were made by halves and were added in 1 ml amounts to 24 ml of sterilized medium (to 23 ml if a substance to be tested for antagonism of antibacterial action was also to be added). Substances to be tested for antagonism of antibacterial action were prepared in sterile aqueous solution and 1 ml of a standard dilution was added to each culture tube of a series containing varying concentrations of the quinone. Acetone and water controls were included in each series. The inoculum of *Escherichia coli* was 0.1 ml of a 24-hour culture in the synthetic medium diluted 1: (approximately 20 to 25 million bacteria, or 800,000 to 1 million per ml of culture). Incubation was at 37° C. except when the volatile ethyl mercaptan was used, when both mercaptan and quinone control series were incubated at 30° C. Readings for bacteriostasis were made daily for 4 to 5 days by observations of visual turbidity. Daily subcultures were made by streaking each culture on an agar plate to determine whether organisms were killed or merely kept from growing.

Nitroprusside tests for sulfhydryl groups were made on mixtures of solutions of quinones and (a) thioglycolic acid neutralized with sodium carbonate and (b) cysteine hydrochloride by adding 3 N NH_3 and a dilute solution of sodium nitroprusside.

RESULTS

Thioglycolic acid neutralized with sodium carbonate and sodium thioglycolate (Eastman) in molar concentrations greater than 2-methyl-1,4-naphthoquinone suppressed both bacteriostatic and bactericidal activity of the quinone on *E. coli* in synthetic medium. This effect might have been due either to their action as reducing agents or to the sulfhydryl groups; consequently other reducing agents were tested. Sodium bisulfite and sodium hydrosulfite partially antagonized

[1] A preliminary report.

[2] W. Thalhimer and B. Palmer, *Jour. Infect. Dis.*, 9: 181, 1911.

[3] E. A. Cooper, *Biochem. Jour.*, 6: 362, 1912.

[4] G. T. Morgan and E. A. Cooper, *Biochem. Jour.*, 15: 587, 1921.

[5] G. T. Morgan and E. A. Cooper, *Soc. Chem. and Ind.*, 43: 352, 1924.

[6] W. D. Armstrong, W. W. Spink and J. Kahnke, *Proc. Soc. Exp. Biol. and Med.*, 53: 230, 1943.

[7] A. E. Oxford and H. Raistrick, *Chem. and Ind.*, 61: 128, 1942.

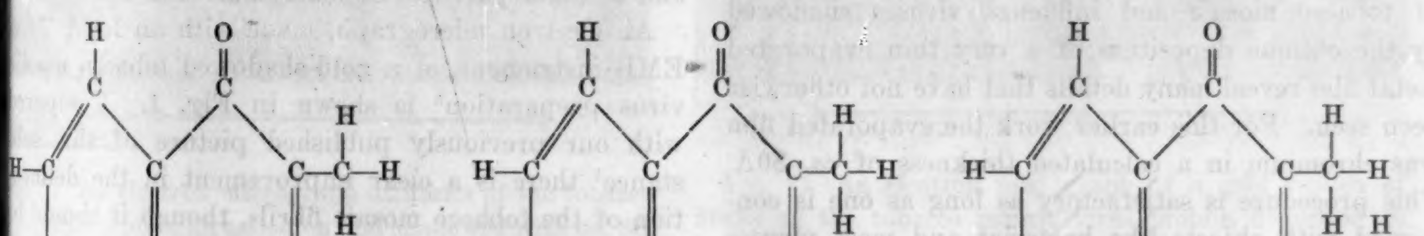
[8] S. A. Waksman and H. B. Woodruff, *Jour. Bact.*, 44: 373, 1942.

[9] Colin McCleod, *Jour. Exp. Med.*, 72: 217, 1940.

the bacteriostatic and bactericidal effects of the quinone, while stannous chloride, potassium formate and sodium thiosulfate had no effect. These results pointed to the probable responsibility of the sulfhydryl group for antagonism noted with thioglycolate; consequently ethyl mercaptan and cysteine hydrochloride were tested. Suppression of anticoli activity of 2-methyl-1,4-naphthoquinone was again noted with these two sulfhydryl compounds.

Sodium thioglycolate and cysteine hydrochloride also antagonized the anticoli activity of 2-methyl-3-chloro-1,4-naphthoquinone, with –Cl instead of –H in the 3 position on the quinone ring, and that of 2,6-dimethyl-1,4-naphthoquinone. However, these sulfhydryl compounds were without effect on the anticoli action of 2-methyl-3-methoxy-1,4-naphthoquinone with the $-OCH_3$ group instead of –H or –Cl in the 3 position.

Nitroprusside tests were difficult to read because of the interfering color of the quinone which masked weakly positive tests. A colored precipitate resulted from the mixture of cysteine and 2-methyl-1,4-naphthoquinone, but not from the mixture of cysteine and the methoxy quinone. As nearly as could be determined under these circumstances, 2-methyl-1,4-naphthoquinone and 2-methyl-3-chloro-1,4-naphthoquinone in excess on a molar basis eliminated the color due to –SH groups in these tests, while 2-methyl-3-methoxy-1,4-naphthoquinone did not, although a slightly weaker color reaction was elicited with the latter compound in excess than in control tests with the same concentration of sulfhydryl.



2-methyl-1,4-naphthoquinone   2-methyl-3-chloro-1,4-naphthoquinone   2-methyl-3-methoxy-1,4-naphthoquinone

Discussion

Interference of sulfhydryl compounds with the antibacterial properties of mercury antiseptics was reported by Fildes in 1940,[10] and a theory of their mode of action was proposed. Nungester, Hood and Warren[11] suggested a practical application of this finding in testing disinfectants of this nature. Thioglycolate, glutathione and cysteine have been found antagonistic to a variety of antibiotic substances including penicidin,[12] penicillin,[13,14] citrinin, gliotoxin, pyocyanin and several from plants,[13] clavicin and penicillic acid.[13,15] Cavallito and Bailey[13] believe that the main mode of action of many antibiotic substances lies in their ability to interfere with the normal function of sulfhydryl groups in bacterial metabolism.

More recently, Geiger and Conn[15] have suggested that since clavicin and penicillic acid are both α, β-unsaturated ketones having as their only common structural detail the $-CH{=}\overset{|}{C}-\overset{|}{C}{=}O$ group, the latter grouping is concerned with their antibacterial potencies. The inactivation of both of these antibiotics, as well as some synthetic, α, β-unsaturated ketones, by sulfhydryl compounds led them to suggest that antibiotic properties of these substances are due to their reaction with sulfhydryl groups essential to the activity of bacterial enzyme systems, or with sulfhydryl-containing metabolites essential to bacteria.

2-methyl-1,4-naphthoquinone may also be considered an α, β-unsaturated ketone, the antibacterial activity of which is suppressed by –SH compounds. Its mode of antibacterial action therefore appears to be similar to that suggested by several groups of investigators for antibiotic substances, some of which are known to contain quinone structures and some not.

The fact that 2-methyl-3-chloro-1,4-naphthoquinone and 2,6-dimethyl-1,4-naphthoquinone with easily replaceable –Cl and –H in the 3 positions on the quinone rings, are also inactivated by sulfhydryl compounds,

[10] Paul Fildes, *Brit. Jour. Exper. Path.*, 21: 67, 1940.

[11] W. J. Nungester, M. N. Hood and M. K. Warren, *Proc. Soc. Exp. Biol. and Med.*, 52: 287, 1943.

[12] N. Atkinson and N. Stanley, *Austral. Jour. Exp. Biol. and Med. Sci.*, 21: 249, 1943.

[13] C. J. Cavallito and J. H. Bailey, Science, 100: 390, 1944.

[14] R. J. Hickey, Science, 101: 232, 1945.

[15] W. B. Geiger and J. E. Conn, *Jour. Amer. Chem. Soc.*, 67: 112, 1945.

while 2-methyl-3-methoxy-1,4-naphthoquinone with the $-OCH_3$ group in that position is not, lends support to the hypothesis that the 3 position on the quinone ring is important in the inhibition of bacterial growth by these compounds. The antibacterial activity of the methoxy quinone, however, even in the presence of sulfhydryl compounds, suggests that the foregoing may be only one of the mechanisms involved.

Details of these studies will be reported in a subsequent communication.

SUMMARY

Thioglycolic acid neutralized with sodium carbonate, sodium thioglycolate (Eastman), ethyl mercaptan, cysteine hydrochloride and certain sulfur-containing reducing agents (sodium bisulfite and sodium hydrosulfite) antagonize the antibacterial action of 2-methyl-1,4-naphthoquinone on *Escherichia coli* in a synthetic medium. Other reducing agents such as stannous chloride, potassium formate and sodium thiosulfate, show no such antagonism. The antibacterial activities of 2-methyl-3-chloro-1,4-naphthoquinone and 2,6-dimethyl-1,4-naphthoquinone are also abolished by excess thioglycolate and cysteine, while that of 2-methyl-3-methoxy-1,4-naphthoquinone with $-OCH_3$ instead of –Cl or –H in the 3 position on the quinone ring, is not. These findings suggest that the mode of antibacterial action of 2-methyl-1,4-naphthoquinone is by blocking essential enzymes through combination with sulfhydryl groups, or through combination with sulfhydryl groups of essential bacterial metabolites. This combination may take place in the 3-position on the quinone ring. This mode of action is similar to that suggested by other investigators for several antibiotic agents including penicillin. The antibacterial activity of the methoxy quinone, however, even in the presence of sulfhydryl groups, suggests that the foregoing explanation may not be the complete one.

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SCIENTIFIC APPARATUS AND LABORATORY METHODS

ELECTRON SHADOW MICROGRAPHY OF THE TOBACCO MOSAIC VIRUS PROTEIN[1,2]

WE have recently shown[3] that electron micrographs of tobacco mosaic and influenza viruses shadowed by the oblique deposition of a very thin evaporated metal film reveal many details that have not otherwise been seen. For this earlier work the evaporated film was chromium in a calculated thickness of *ca.* 80A. This procedure is satisfactory as long as one is concerned with objects like bacteria[4] and most viruses that are large compared with the thickness of the metallic layer deposited on them during shadowing. In attempts to detect very small particles it has been found that they may be recorded, though smaller in diameter than the thickness of chromium they accumulate when shadowed. Though this does not in itself interfere with their detection, it gives an obviously false impression of shape and renders difficult and inaccurate any measurements of their true size. We have accordingly sought a metal of higher electronic scattering power than chromium which would give continuous films upon evaporation and could therefore be used in much thinner layers for shadowing. Gold in a calculated thickness of 5 to 10A meets these requirements. It replaces chromium to great advantage in the photography of the smallest viruses and of other particles of macromolecular size.

An electron micrograph, made with an RCA Type EMB instrument, of a gold-shadowed tobacco mosaic virus preparation[5] is shown in Fig. 1. Compared with our previously published picture of this substance[3] there is a clear improvement in the delineation of the tobacco mosaic fibrils, though it should be emphasized that when allowance is made for the different thicknesses of the coating metals the same general idea of fibril-shape emerges from a consideration of each photograph. There is also a reduction in the texture of the background detail which has its origin in the ultimate structure of the collodion substrate. This reduction is important for work with other macromolecules because such molecules can be studied on collodion substrates only as long as a discrimination can be made on the photographs between the macromolecules and the structural details of collodion.

Since, as the figure indicates, collodion has an ultimate structure approaching in dimensions the width of the tobacco mosaic virus molecule and since far smaller particles can be recognized through shadow-casting, it has been important to find and utilize a

1 From the Department of Physics and the Virus Laboratory, Department of Epidemiology, School of Public Health, University of Michigan.

2 Supported in part by a grant from the National Foundation for Infantile Paralysis, Inc.

3 R. C. Williams and R. W. G. Wyckoff, *Proc. Soc. Exp. Biol. and Med.*, 58: 265, 1945.

4 R. C. Williams and R. W. G. Wyckoff. In press.

5 We are indebted to W. M. Stanley for the purified tobacco mosaic virus protein used in this work.

oother substrate. Polished glass has such a smooth-ss, and we have found that replica preparations de in the following fashion reproduce particles macromolecular dimensions spread upon its sur-ce. To make these replicas of purified tobacco saic protein, a drop of an appropriate dilution in tilled water is first placed on a chemically cleaned croscope slide. This slide, when thoroughly dry,

IG. 1. An electron micrograph of fibrils of the tobacco aic virus protein on collodion and shadowed with *ca.* 8A gold. The lines drawn at the bottom of this and the t figure are each one micron long. This magnification been established by the photography of an all-metal lica of a 15,000 line per inch diffraction grating. se two figures are negatives; they have been prepared reproduction by making contact positives from the inal negatives on medium lantern-slide plates and ting from them onto No. 3 Bromide paper.

placed in the vacuum chamber of the evaporating fit and coated with a calculated average thickness *ca.* 8A of gold, the angle of deposition being such t the lengths of the shadows are several times the ghts of the objects causing them. On removal from vacuum chamber the regions of the metal-coated e intended for study are immediately covered with in (*ca.* 500A) layer of collodion. As soon as it is , this film and its adhering gold is stripped from glass onto the customary wire specimen screen h the help of "Scotch tape," following procedures commonly employed in handling replicas for metallographic examination. Because of the predominant scattering power of the gold, it makes little difference whether the small organic particles actually leave the glass when the replica is stripped. The collodion film now shows no structure when examined in the microscope because its fine structure has not been brought out by the shadow-cast gold. Fig. 2 is a

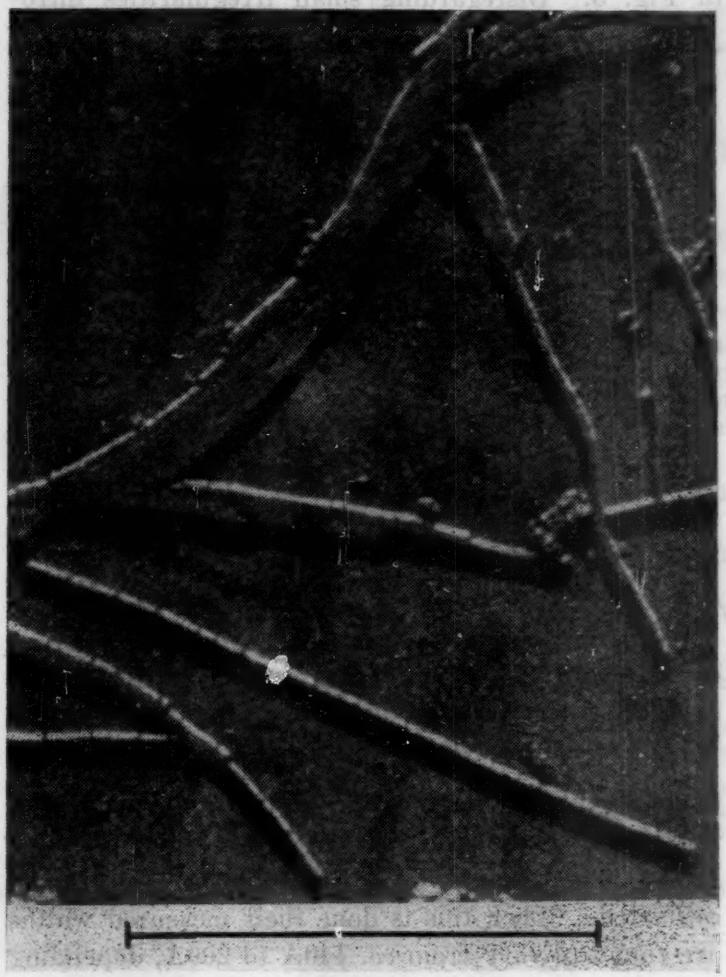

FIG. 2. An electron micrograph of a gold replica of fibrils of the tobacco mosaic virus protein deposited on glass. The same details of fibril structure appear on the two photographs, but the greater background smoothness of the glass surface is apparent.

photograph of such a stripped gold replica of tobacco mosaic fibrils lying on a glass surface.

A careful comparison of these two photographs and of others like them has demonstrated that there is no detectable difference in appearance or dimensions between the tobacco mosaic fibrils seen in the replicas or shadowed directly on collodion. The fine details of structure of the tobacco mosaic rods, as exemplified by their parallel groupings and by the segmentation of their separate elements, appear at least as well in the replica as in Fig. 1. This apparent faithfulness of the replica and the far greater smoothness of its background make certain that it can be used to reveal macromolecules much smaller than those of the tobacco mosaic protein.

Photographs such as those reproduced above pro-

vide a measure of both the breadths and the heights of individual tobacco mosaic fibrils. Since the separate rods are easily distinguished from one another as they lie parallel and closely packed in bundles, they can be counted and their total width measured. This can be done with accuracy by photometering across the parallel clusters of fibrils that appear in both figures. Such a photometric traverse is given in Fig. 3. Disregarding small irregularities intro-

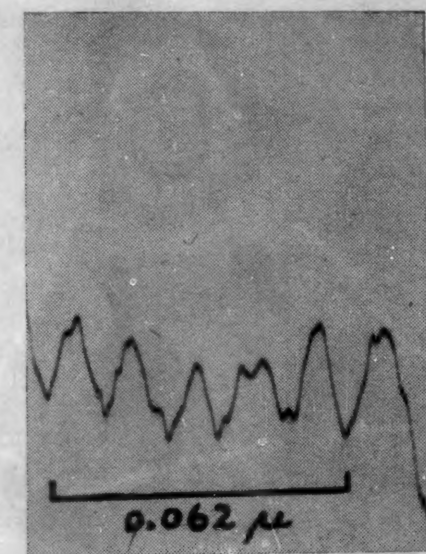

FIG. 3. A microphotometric record of a traverse normal to the length of a group of five parallel fibrils. As the appended scale of magnification indicates, this corresponds to a linear magnification of about half a million.

duced by photographic grain at this high magnification, it is seen that the fibres have a uniform width of 125A. The breadth of isolated fibrils can also be estimated. When this is done their measured widths are found to vary from *ca.* 140A to 200A, depending on their orientation with respect to the direction of shadowing. As would be expected, the apparent breadth is greatest for those that lie about normal to the direction of metal evaporation. Rods that lie parallel to this direction cast no lateral shadows and are so poorly visible that their widths can not be measured accurately; but upon plotting apparent widths as a function of angle of deposition for the other rods, it is found that the unshadowed fibrils must have a breadth close to *ca.* 120A. Hence the width of a fibril is substantially the same, whether it is lying alone or as a member of an oriented bundle. This has importance in connection with problems involving the changes in shape and size that these and other macromolecules may suffer during desiccation. The breadths we have measured above are comparable with previous estimates of 150A based on direct electron micrography.[6]

The height of a tobacco mosaic fibril can be deduced

[6] W. M. Stanley and T. F. Anderson, *Jour. Biol. Chem.*, 139: 325, 1941.

from a knowledge of the length of the shadow it ca and the angle between the shadowing atomic beam a the shadowed surface. Collodion films mounted the wire screens used for electron micrography not flat, and this has made it difficult to know acc rately the angle of shadowing at a given point them; but this uncertainty no longer exists wh dealing with replicas taken from a flat glass surfa The replica of Fig. 2 was made so that shad lengths are five times the heights of the objects ca ing them. The lengths of the shadows of the toba mosaic fibrils are best measured from the shadow edge of groups of rods lying normal to the directi of evaporation. Such shadows prove to be *ca.* 600 long. The fibrils then are one fifth of this, or 120 high; they are thus of equal width and height.

Individual fibrils, of which the one lying horiz tally at the bottom of Fig. 2 is a good examp often appear segmented along their lengths. It h been suggested[6] that the lengths of individual tobac mosaic rods as observed in the electron microsc are integral multiples of some unit that could considered as the fundamental molecular length. W have examined many of the segments seen in o photographs to determine whether their lengths a either uniform or simple multiples of an underlyi unit. They vary in an apparently continuous m ner between *ca.* 200A and *ca.* 1,000A.

SUMMARY

Two improvements are described in the use shadow electron micrography for the observation particles of macromolecular dimensions. One invol the substitution of gold for chromium as shadow metal. The thinner gold film that can be employ gives a truer representation of the shape of partic so small that shape and size are significantly alter by the thickness of the shadowing metal deposited them. The other consists in metal-shadowing su particles deposited on a very smooth surface such that of polished glass and the handling of this me film as a replica of the glass surface and the p ticles resting on it. This technique permits photography of particles whose direct observation disturbed by the fine structure that is brought by shadowing a collodion substrate. Application these methods to the electron micrography of tobacco mosaic virus protein shows that its fibrils rods about 125A both in height and breadth. Tho the rods appear segmented, these segments have been found to have a length that is constant or small integral multiple of an underlying unit.

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